CLINICAL STUDY PROTOCOL

Primary study intervention	Gepotidacin
Other study intervention	None
Study identifier	219575
IND number	111885
Approval date	10 Sep 2024
Title	A Phase 3b, open-label, single-arm study in adolescent and adult female participants to evaluate clinical symptom improvement and the safety of gepotidacin during treatment of uncomplicated urinary tract infections (acute cystitis)
Compound number/name	GSK2140944/gepotidacin
Brief title	A study in adolescent and adult female participants to evaluate clinical symptom improvement and the safety of gepotidacin during treatment of uncomplicated urinary tract infections (acute cystitis)
Sponsor	GSK 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Sponsor signatory	Dr Aruni Mulgirigama, MBBS, MRCP, MFPM Global Medical Affairs Leader, Antibiotics GSK General Medicines

Medical monitor name and contact can be found in local study contact information document.

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK/PPD.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with Good Clinical Practices and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK/PPD and the express physical and/or digital informed consent of the participant and/or the participant's legally authorized representative.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To cooperate with representative(s) of GSK/PPD in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK/PPD will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK/PPD with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK/PPD may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK/PPD with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

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Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	10 Sep 2024
Original Protocol	27 June 2023

Amendment 1 (10 Sep 2024)

This global amendment is considered to be substantial.

Overall Rationale for the Amendment: This global amendment covers the following:

i. Clarifies a perceived ambiguity about number of measurements of the clinical symptoms score at baseline,

ii. Remove need to send a stool sample to central laboratory for confirmation testing of Clostridium difficile which is now confirmed by testing at local laboratories,

iii. Remove reflex testing with urine culture from the urinalysis performed at baseline.

iv. Adjust pregnancy notification form from a paper method to electronic and additional minor wording edits.

Section # and Name	Description of Change	Brief Rationale
Section 1.2. Schema Figure 1. Study design overview. Footnote a. Section 1.3. Schedule of Activities (SoA). Table 1. Footnote a and n. Section 4. Study design 4.1 Overall design. Section 8. Study assessment and procedures. Section 8.2.1. Clinical Symptom score and clinical outcomes. Section 10.1. Appendix 1. Clinical symptom score for uUTI.	Rewording of the CSS assessment procedure performed at baseline. Clarification that only one baseline CSS assessment will be performed. To clarify procedures performed by VRCC and Study staff while assessing CSS at the different visit calls.	Clarifies a perceived ambiguity about number of measurements of the clinical symptoms score at baseline. Clarifies a perceived ambiguity on responsible person performing the CSS at each visit.
Section 10.6 Appendix 6. CDAD Testing and procedure, algorithm, and process flow.	Remove need to send a stool sample to central laboratory for confirmation testing of *Clostridium difficile* which is now confirmed by testing at local laboratories.	Protocol instructs to send a frozen sample to IHMA central laboratory, however based on (1) learnings from recently completed phase 3 studies (EAGLE-1, -2 and -3) and (2) the current capabilities of *C. difficile* testing in local laboratories, recommendation is to follow the local laboratory *C. difficile* testing algorithm that is currently in the protocol but omitting the

		confirmatory *C. difficile* testing at IHMA. Sites should send stool samples for *C. difficile* testing to their local or reference laboratory for testing according to the algorithm in the protocol.
Section 10.7 Appendix 7. Clinical laboratory tests. Table 9. Protocol-required clinical safety laboratory tests.	Remove reflex testing with urine culture from the urinalysis performed at baseline.	Correction of typographical error. Consistency with the planned statistical analysis and required outputs.
Section 8.4.5 Regulatory reporting requirements for SAEs. Table 6. Timeframes for submitting SAEs, pregnancy and other events reports to GSK. Section 8.4.8 Contact information for reporting SAEs and pregnancies – Pregnancy event reporting.	Adjust pregnancy notification form from a paper method to electronic.	Collection of pregnancy information, instruct to submit a paper pregnancy notification report at 24 hours and at follow up, however based on (1) internal process optimization and (2) sustainability, the paper pregnancy notification report will be replaced by an electronic pregnancy notification report. These electronic pregnancy notification reports will be part of the eCRF which should be completed following the instructions provided in the protocol and the eCRF completion guidance.
Section. Introduction 2.1. Study rationale.	Superiority is changed to Non inferiority to accurately describe the primary objective of the global phase 3 studies and clarified reference to superiority met in study 212390.	Correction of typographical error
Section 10.7. Appendix 7: Clinical Laboratory Test	Removal of mention to laboratory results that could unblind the study, considered not applicable for this open label study.	Correction of typographical error
Section 1.3. Schedule of Activities (SoA). Table 1. Footnote o.	To clarify removal of mention of not being required to collect the number of doses taken and the CSS assessment after the Visit 2 assessment, part of secondary objectives, needed for compliance.	Consistency with the planned statistical analysis and required outputs.
Section 10.1. Appendix 1. Clinical symptoms score of uUTI	To clarify CSS assessment is not performed at Visit 7.	Correction of typographical error. Consistency with SoA.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AChE-I	Acetylcholinesterase inhibition
AE	Adverse event
AESI	Adverse event of special interest
CCI [redacted]	
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the drug concentration-time curve
BID	Twice daily
BMI	Body mass index
CDAD	*Clostridioides difficile*-associated diarrhea
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum concentration
CSR	Clinical study report
CSS	Clinical Symptom Score
CV	Cardiovascular
CYP3A4	Cytochrome P450 enzyme 3A4
DAIDS	Division of AIDS
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Early discontinuation
EDC	Electronic data capture
ePIP	Electronic Protocol Inquiry Platform
ER	Extended release
ESBL	Extended-spectrum β-lactamase
ESRD	End-stage renal disease
FPFV	First participant first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
h	Hours
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HRT	Hormone replacement therapy
IAF	Informed assent form
IB	Investigator's brochure
ICE	Intercurrent events
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IgM	Immunoglobulin M

Abbreviation	Definition
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent-to-Treat
IV	Intravenous
LAR	Legally authorized representative
LFT	Liver function test
MDR	Multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PK	Pharmacokinetic
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTL	Quality tolerance limit
SAE	Serious adverse event
SDV/SDR	Source Data Verification/Source Document Review
SoA	Schedule of activities
SRT	Safety Review Team
TdP	Torsades de pointes
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UTI	Urinary tract infection
uUTI	Uncomplicated urinary tract infection
VRCC	Virtual Research Coordination Center
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol title: A Phase 3b, open-label, single-arm study in adolescent and adult female participants to evaluate clinical symptom improvement and the safety of gepotidacin during treatment of uncomplicated urinary tract infections (acute cystitis)

Brief title: A study in adolescent and adult female participants to evaluate clinical symptom improvement and the safety of gepotidacin during treatment of uncomplicated urinary tract infections (acute cystitis)

Rationale: uUTIs affect the quality of life of patients. Feedback from patients and medical providers has demonstrated the need to better assess the burden of UTIs in women and early clinical symptom improvement on a daily basis.

The Phase 3 gepotidacin studies conducted in uUTI (Section 2.2) were conducted based on the need to identify new and effective oral antibiotic treatment options for uUTI, as such therapies are becoming limited due to the increase of MDR uropathogens and ESBL-producing Enterobacterales uropathogens, which are impacting the efficacy of the currently available oral antibacterial treatment options. The studies focused on a primary therapeutic response composite endpoint of both clinical resolution and microbiological eradication, which were measured at specific time points, in line with regulatory guidance [DHHS, 2019].

However, the Phase 3 studies did not measure symptom improvement on a daily basis after the start of study intervention to characterize the time profile of change in clinical symptomatology improvement. The present study will align with the study design and treatment aspects of the gepotidacin Phase 3 studies [Perry, 2022]; however, it will focus primarily on clinical symptom improvement in participants with a uUTI by assessing the CSS on a daily basis after the start of and during gepotidacin treatment. This study data will provide additional clinical data for gepotidacin in uUTIs.

Refer to Section 2.1 for additional information on the study rationale and Section 4.2 for additional information on the rationale for study design.

Objectives, endpoints, and estimands: The primary objective of this study is to evaluate the clinical symptom improvement with gepotidacin treatment in female participants with uUTI at (24 hours [±4 hours]). This will be evaluated by the number of participants who achieve clinical symptom improvement (without the need for other systemic antimicrobials), defined as a decrease from Baseline in CSS total score of at least 1 point at (24 hours [±4 hours]). For additional information on the primary, secondary, and exploratory objectives and endpoints, refer to Section 3.

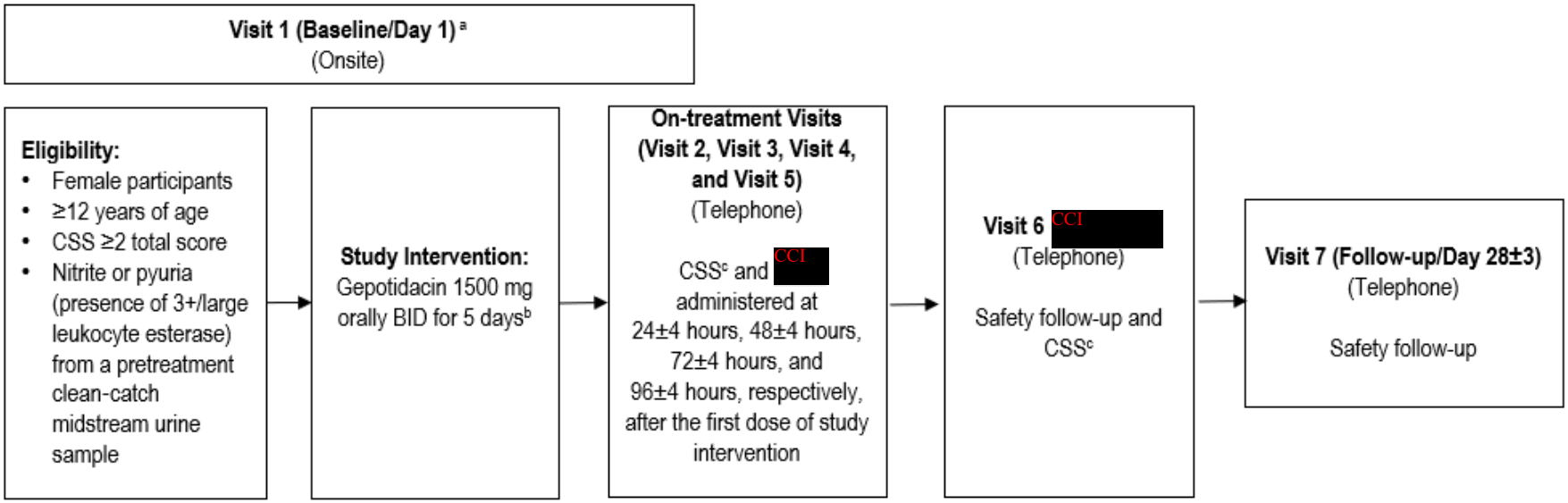
Overall design: This is a Phase 3b, open-label, single-arm, multicenter study to evaluate clinical symptom improvement and the safety of gepotidacin in female participants ≥12 years of age with clinical symptoms and urine dipstick findings suggestive of uUTI. Participants who meet eligibility requirements will receive gepotidacin 1500 mg administered orally as 2 × 750 mg tablets BID for 5 days. (Note: Each dose is to be taken after food consumption and with water to assist with tolerability.) Clinical symptom and safety assessments will be conducted throughout the study. The total duration of study participation is approximately 28 days, with at least 1 planned on site study visit and 6 telephone call study contacts (see Section 1.3 and Section 8 for study visit details), with allowance for unscheduled visits. For additional information on the overall design, refer to Section 4.1.

Number of participants: Approximately 90 participants will be enrolled in the study to ensure at least 82 evaluable participants are included in the primary analysis, such that the half width of the 95% CI is approximately ≤10%, under an assumption that 74% of participants meet the primary endpoint criteria as observed in the Phase 3 studies.

Data monitoring/other committee: This will be overseen by the GSK SRT (Section 10.9.6).

1.2. Schema

Figure 1 Study design overview



a. During Visit 1, prior to first dose of study intervention, the Virtual Research Coordination Center (VRCC) will contact the participant by telephone to perform the CSS assessment and CCI CCI (in that specific order). This will be used as the Baseline CSS. The CSS will be reviewed (but not remeasured) by a study physician or otherwise appropriate medically trained staff from the study site onsite along with determination of whether other eligibility criteria are met before the first dose of study medication. Only If VRCC cannot do the telephone call, then the study physician or otherwise appropriate medically trained staff from the study site will ask the CSS questions and complete the CCI CCI before the first dose of study intervention. Only one CSS and CCI is to be performed at Visit 1.

b. The first dose of study intervention will be administered at the study site during Visit 1; the remaining 9 doses over the 5-day treatment course will be self-administered as outpatients. Each dose is to be taken after food consumption and with water to assist with tolerability.

c. At Visit 2, Visit 3, Visit 4, and Visit 5, the CSS assessment and CCI CCI will be completed (in that order) by VRCC. CCI [redacted].

1.3. Schedule of activities (SoA)

Table 1 Schedule of activities

Visit[a, b, d]	Baseline/Day 1		On-treatment				Follow-up		Unscheduled[c]	Early Withdrawal[e]
	1		2	3	4	5	6	7		
Window[f]	Predose	Postdose	24±4 h	48±4 h	72±4 h	96±4 h	CCI	28 days (±3 days)		
Mode of Visit[b]	Onsite	Onsite	Telephone call	Telephone call	Telephone call	Telephone call	Telephone call	Telephone call	(Onsite or Telephone)	(Onsite or Telephone)
Procedure										
Documented informed consent/assent	X									
Inclusion and exclusion criteria	X									
Participant demography	X									
Physical examination[g]	X								X	
Medical, uUTI, and surgical history	X									
Urine dipstick[h]	X								X	
Hematology, chemistry, and urinalysis[i]	X								X	
Drug and alcohol screen[i]	X									
12-lead ECG	X								X	
Vital sign measurements[j]	X								X	
Urine pregnancy test[i, k]	X			X						
Telephone call completed by VRCC[l]	X		X	X	X	X				
Safety telephone call completed by the study site[m]							X	X	X	X
CCI	X[n]		X[o]	X	X	X	X		X	X
	X[p]		X	X	X	X			X	X

Visit[a, b, d]	Baseline/Day 1		On-treatment				Follow-up		Unscheduled[c]	Early Withdrawal[e]
	1		2	3	4	5	6	7		
Window[f]	Predose	Postdose	24±4 h	48±4 h	72±4 h	96±4 h	CCI	28 days (±3 days)		
Mode of Visit[b]	Onsite	Onsite	Telephone call	Telephone call	Telephone call	Telephone call	Telephone call	Telephone call	(Onsite or Telephone)	(Onsite or Telephone)
Study intervention dosing[q]		X	X	X	X	X				
SAEs[r]	X	←	—	—	—	—	—	—	—	→
AEs[s]		←	—	—	—	—	—	—	—	→
Prior/concomitant medication review[t]	X	X	X	X	X	X	X	X	X	X
Study intervention compliance[u]			X	X	X	X				
Schedule next visit/telephone visit[v]	X		X	X	X	X	X			

a. Prescreening activities may also be conducted, including a prescreening informed consent and urine testing, as detailed in Section 8. The Visit 1 telephone call to assess CSS and CCI (in that specific order) will be conducted by VRCC when the participant is onsite. The CSS will be reviewed (but not remeasured) by a study physician or otherwise appropriate medically trained staff from the study site onsite along with determination of whether other eligibility criteria are met before the first dose of study medication. Only if VRCC cannot do the telephone call, then the study physician or otherwise appropriate medically trained staff from the study site will ask the CSS questions and complete the CCI CCI before the first dose of study intervention. Only one CSS and CCI is to be performed at Visit 1

b. All planned postbaseline visits (i.e., On-treatment and Follow-up) are telephone visits. The study physician or otherwise appropriate medically trained staff from the study site will conduct a safety telephone visit at Visit 6 and Visit 7. VRCC will conduct the visits at Visit 1, Visit 2, Visit 3, Visit 4, and Visit 5 and assess CSS and CCI (in that specific order).

c. An onsite or telephone Unscheduled Visit will be arranged at any point during the study if there are safety concerns or a lack of response to study intervention or for early withdrawal. An alternative antibiotic therapy may be prescribed/administered at the Unscheduled Visit. Additional investigations may be performed per investigator discretion.

d. Each treatment visit will be assessed over a 24-hour period, starting with the first dose of study intervention received for an individual participant. For example, participants who only receive 1 dose of study intervention on their first calendar day in the study due to a late afternoon/evening Visit 1 will take the second dose on the following calendar day. This pattern will continue until all 10 doses are received; thus, the tenth/last dose will be taken prior to Visit 5 (may be 5 or 6 calendar days, depending on when the first dose is taken).

e. Early withdrawal visits may be performed onsite and/or via telephone as needed; this will be determined by the medical monitor. If the Early Withdrawal Visit occurs before the end of On-treatment (Visit 5), then the CSS assessment and CCI CCI will be collected. If a participant withdraws early from the study prior to Visit 7, then the Visit 7 assessments will be performed as the Early Withdrawal Visit. If the Early Withdrawal Visit is not performed, then the whole visit will not be active in the EDC (even if participant decided to terminate participation and the visit was to have been done).

f. The start of each time window is the time from the first dose of study intervention taken.

g. If an additional physical examination is performed (i.e., Unscheduled Visit), it may be symptom directed, and any clinically significant changes from Baseline or clinically significant new clinical signs will be reported as AEs.

h. Participants will provide a predose, clean-catch, midstream urine sample for a urine dipstick test to confirm nitrite or pyuria (presence of 3+/large leukocyte esterase) based on local laboratory procedures. See Section 8.3.4 for additional information.
i. With the exception of the urine dipstick and baseline pregnancy testing, a central laboratory will be used. Any baseline results received while participants are On-treatment that are exclusionary will be assessed by the medical monitor. The medical monitor will contact the investigator and advise on appropriate action with the study intervention.
j. Measure temperature, blood pressure, respiratory rate, and pulse rate. See Section 8.3.2 for additional details.
k. For women of childbearing potential, a negative high sensitivity urine pregnancy test is sufficient for eligibility. A pregnancy test will be performed predose and just before taking the fifth dose. The pregnancy test before the fifth dose will be done at home using a test kit supplied at Baseline, with the result confirmed at Visit 4.
l. VRCC will confirm the doses of study intervention taken the previous day and results of at home pregnancy tests. AEs will not directly be asked about by VRCC, and VRCC will direct any AEs, SAEs, or concomitant medications reported during telephone visits directly to the study site; the study physician or otherwise appropriate medically trained staff from the study site will follow-up with the participant.
m. The study physician or otherwise appropriate medically trained staff from the study site will perform a safety telephone call at Visit 6 CCI), and at Visit 7 (±3 days). The study physician or otherwise appropriate medically trained staff from the study site will follow-up with participants who report an AE, SAE, or use of a concomitant medication to VRCC.
n. CCI [redacted]
o. Participants must have taken 2 doses of study intervention before the Visit 2 CSS telephone assessment. This will be confirmed during the Visit 2 telephone call. For any participants who have not received 2 doses of study intervention, a second telephone call will be scheduled to perform the CSS after the second dose has been taken.
p. The CCI CCI will be administered to participants via a telephone interview performed by VRCC. These assessments will be performed by the same interviewer who determines the CSS. See Section 8.2.2 for additional information.
q. The first dose of study intervention will be administered at the study site during Visit 1; the remaining 9 doses over the 5-day treatment course will be self-administered as outpatients. Each dose is to be taken after food consumption and with water to assist with tolerability. The third dose of study intervention cannot be taken until the Visit 2 assessments have been completed.
r. Record SAEs from the start of study intervention. However, SAEs assessed as related to study participation or related to GSK product (non-IMP) will be recorded from the time of consent/assent. See Section 8.4.1 for details. During any postbaseline visit, if a participant reports an SAE, VRCC will refer the participant to the study site to record the SAE.
s. Record AEs from the time of the first dose of study intervention. During any postbaseline VRCC telephone calls, if a participant reports an AE, VRCC will refer the participant to the study site to record the AE.
t. Prior and concomitant medications will be collected and reviewed throughout the study. During any postbaseline visits if a participant reports concomitant medication use, VRCC will refer the participant to the study site to record the concomitant medication.
u. Study intervention compliance will be determined via telephone on a daily basis. VRCC will ask the participant how many tablets have been taken and/or are remaining. Participants will return study intervention to the study site by Visit 7 using a prepaid envelope provided by the study site.
v. Schedule the date and time of the next telephone visit.

2. INTRODUCTION

Gepotidacin (GSK21409144) is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action and binding site [Bax, 2010; Gibson, 2019] and provides well-balanced inhibition of 2 different type II topoisomerase enzymes [Oviatt, 2022]. This provides activity against most strains of target uUTI uropathogens, such as *Escherichia coli* and *Staphylococcus saprophyticus*, including isolates resistant to current antibiotics [Biedenbach, 2016; Mushtaq, 2019]. Due to well-balanced binding at both enzymes, mutations in both enzymes are needed to significantly affect gepotidacin susceptibility [Oviatt, 2022].

uUTIs, also referred to as acute cystitis, are defined as UTIs in nonpregnant female patients with no known urological abnormalities or complicating comorbidities and not accompanied by signs or symptoms suggesting systemic (i.e., not localized to the bladder) infection, such as fever or costovertebral angle pain [Gupta, 2011; DHHS, 2019]. Common symptoms of uUTIs are pain on urination (dysuria), frequent urination (frequency), sudden onset of the need to urinate (urgency), pain in the lower abdomen (suprapubic pain), inability to start the urine stream (hesitancy), and cloudy urine or blood in the urine (hematuria). In addition to the physical symptoms, uUTIs have been shown to affect a patient's quality of life and their emotional and mental health [Grigoryan, 2022].

2.1. Study rationale

The patient burden of uUTI is significant, with each episode of uUTI associated with approximately 6 symptomatic days, 2 to 3 days of restricted activity, and an unknown amount of time lost from work. Most of the symptoms experienced by patients were rated as moderate to severe in intensity and some of them were the most common associated with impairment of daily living. There is a need to better assess the burden of UTIs in women because few data are available that describe patient-reported outcomes regarding time to improvement and resolution of uUTI symptoms. Feedback from patients and providers states that patients want to feel better after the first dose of treatment and it has been shown that rapid reversal of the overall severity of uUTI symptoms allows the patient to resume normal work/social activities [Klimberg, 2005].

The Phase 3 gepotidacin studies conducted in uUTI (Section 2.2) were conducted based on the need to identify new and effective oral antibiotic treatment options for uUTIs, as such therapies are becoming limited due to the increase in MDR pathogens and ESBL-producing Enterobacterales pathogens, which are impacting the efficacy of the currently available oral antibacterial treatment options (see Section 2.2).

More recently, two Phase 3 clinical studies (Study 204989 and Study 212390) that assessed gepotidacin (1500 mg BID for 5 days) compared with nitrofurantoin (100 mg BID for 5 days) in uUTI showed gepotidacin was non-inferior in the primary therapeutic response evaluated at a preplanned interim analysis in both studies and superior to nitrofurantoin in study 212390. Full data analyses and reporting activities are complete [Study 204989, (NCT04020341); Study 212390, (NCT04187144); Hall, 2023] for both Phase 3 trials.

The Phase 3 primary endpoint in the studies was a composite of both clinical and microbiological success captured at the Test of Cure Visit, 10 to 13 days after randomization. CCI [redacted]
CCI [redacted]
CCI [redacted]

The purpose of this Phase 3b study for gepotidacin in female participants with uUTI is to evaluate clinical symptom improvement on each day during the 5-day treatment period, specifically including the 24-hour time point. The microbiological components of uUTIs were fully assessed in Study 204989 and Study 212390. These additional data are expected to align with current clinical practice and to inform practitioners on the potential use of gepotidacin in uUTIs.

2.2. Background

UTIs are one of the most common bacterial outpatient infections, with a lifetime incidence of 50% to 60% in adult females [Medina, 2019]. An estimated 11% of adult females experience at least 1 episode of uUTI per year, with half experiencing more than 1 recurrent episode over their lifetime [Foxman, 2000]. Apart from a spike in young sexually active women, the incidence of uUTIs generally increases with age [Fihn, 2003; Schmiemann, 2010; Suskind, 2016].

The predominant uropathogen isolated in community-acquired UTIs is *E. coli* (approximately 75%) [Foxman, 2010; Foxman, 2014; Flores-Mireles, 2015]. Other uropathogens, including *Staphylococcus*, *Enterococcus*, *Klebsiella*, and *Proteus* species, are less common collectively, accounting for approximately 20% of uropathogens isolated in community-acquired UTIs [Foxman, 2010; Flores-Mireles, 2015].

Existing oral therapies for uUTI are becoming increasingly limited due to rising trends for MDR pathogens, including ESBL-producing Enterobacterales, which are impacting the efficacy of currently available oral antimicrobial treatment options. Treatment options are further limited for patients with an antibiotic allergy or intolerance or comorbidities such as renal impairment. Thus, there is an increasingly urgent unmet medical need for new therapeutic agents for the treatment of uUTI, particularly those with potent activity against MDR *E. coli* urinary pathogens and with a low propensity for collateral damage [Abadi, 2019; CDC, 2019; ECDC, 2022; Spellberg, 2015].

Gepotidacin has demonstrated activity against most strains of target uUTI uropathogens including *E. coli* and *S. saprophyticus*, including isolates resistant to current antibiotics [Biedenbach, 2016; Mushtaq, 2019]. With its ability to selectively inhibit 2 bacterial DNA enzymes, DNA gyrase, and topoisomerase 4, by a unique mechanism that is not utilized by any currently approved human therapeutic agent [Bax, 2010; Gibson, 2019], gepotidacin has the potential to address a significant and burgeoning unmet medical need by providing a new and effective oral treatment option for uUTI that might obviate the need for IV treatment.

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

2.3. Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of gepotidacin may be found in the IB.

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gepotidacin (GSK2140944)		
Cardiovascular Effects Based on nonclinical data, cardiovascular effects were reversible increases in heart rate and blood pressure (dog and monkey); a 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 h 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 h after the end of the infusion (see Section 5.2.6 and Section 6 of the IB). In Phase 1 and 2 studies, concentration-dependent QT prolongation has been observed during clinical trials with gepotidacin; however, this increase has not translated into medically significant QTc values or changes from Baseline (QTcF >500 msec or change from Baseline >60 msec) or cardiovascular safety concerns. In Phase 1 and 2 studies, gepotidacin did not have a clinically relevant effect on cardiac conduction (PR and QRS intervals).	See Section 5.2 for excluded cardiac conditions. Close monitoring of clinical parameters and AEs (Section 1.3) will be conducted, and treatment monitoring and evaluation criteria (Section 7.1.2) will be utilized to mitigate cardiovascular effects. Participants taking medications known to increase QT or potent CYP3A4 inhibitors will be excluded (see Section 6.9.2). See also the Renal and Hepatic sections in 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 non-glandular 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 in this table below. Clostridioides difficile-associated diarrhea (CDAD) has been observed in clinical trials with gepotidacin.	See Section 5.2 for excluded medical conditions. Close monitoring of clinical parameters and AEs (Section 1.3) will be conducted to mitigate and assess gastrointestinal effects. Suspected CDAD will be managed according to a prespecified algorithm provided in Appendix Section 10.6.
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. AEs possibly consistent with AChE-I, including diarrhea, nausea, vomiting, gastrointestinal cramping and pain, dyspnea, bradycardia, lacrimation, salivation, dysarthria, and	Participants who have medical conditions or require medications that may be impacted by inhibition of acetylcholinesterase will be excluded from participation in this study. See Section 5.2 for excluded medical conditions and Section 6.9.2, for prohibited medications. Close monitoring of clinical parameters and AEs will be conducted to assess effects potentially related to acetylcholinesterase inhibition (Section 1.3).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	diaphoresis/sweating, have been reported during clinical trials with gepotidacin. The majority of these AEs have been mild and transient and have been reported in clinical trials with comparable Cmax levels expected in this study. The majority of events potentially caused by AChE-I were nonserious AEs and none were of a life-threatening nature (e.g., heart block). Most AChE events have been driven by gastrointestinal events.	
Hepatic Effects In preclinical studies, increases in liver enzymes and total bilirubin were observed in some rats at or above clinical exposure, in the absence of microscopic evidence of liver toxicity. Additionally, the weight of evidence, including studies in dogs and monkeys, suggests a low likelihood of liver toxicity in humans.	In Phase 1 and 2 studies, 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 have not been suggestive of an adverse effect of gepotidacin, and none were considered related to study treatment.	Participants with severe hepatic impairment are excluded. See Section 5.2 for excluded medical conditions. Monitoring and stopping criteria liver events have been implemented.
Use in participants with hepatic dysfunction	A substantial increase in Cmax and AUC and a decrease in clearance were observed in volunteer participants with severe hepatic impairment.	Specific exclusion criteria related to liver conditions and laboratory results have been implemented in the protocol. Monitoring, including chemistry testing during treatment, and stopping criteria have been implemented as per protocol.

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.	Participants with severe renal impairment/ESRD (including those who may require dialysis) are excluded. See Section 5.2 for excluded medical conditions. Monitoring criteria have been implemented.
Use in participants with renal dysfunction	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).	Specific exclusion criteria related to renal conditions and laboratory results have been implemented in the protocol.

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 not recommended in pregnant or nursing mothers. Pregnancy testing requirements in this study minimize the risk of exposure to a fetus. See Appendix Section 10.3 for contraceptive measures and for required pregnancy testing.

2.3.2. Benefit assessment

uUTI is among the most common indications for which antimicrobials are prescribed for otherwise healthy women [Gupta, 2011]. 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 uropathogen in uUTI, *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 uUTI.

In addition to routine medical monitoring appropriate for uUTI, participants will receive heightened monitoring to ensure safety when participating in a clinical study.

2.3.3. Overall benefit-risk conclusion

Antimicrobial resistance among uropathogens causing uUTI has increased in the past decades [Gupta, 2011; 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 that are not utilized by any currently approved human therapeutic agent.

Two Phase 3 clinical studies (Study 204989 [NCT04020341] and Study 212390 [NCT04187144]) that assessed gepotidacin (1500 mg BID for 5 days) compared with nitrofurantoin (100 mg BID for 5 days) in uUTI recently stopped early after an interim analysis showed noninferiority in the primary efficacy endpoint of therapeutic response with no safety concerns identified by the Independent Data Monitoring Committee. In the Phase 3 studies, no new safety or tolerability concerns were identified from AEs. Very few SAEs were observed in the Phase 3 studies. There was a higher frequency of gastrointestinal AEs in the gepotidacin arm compared with the nitrofurantoin arm, which was expected based on the Phase 1/2 gepotidacin data and nitrofurantoin label; diarrhea was the most common AE overall and the most common gastrointestinal AE in the gepotidacin arm compared with the nitrofurantoin arm, and the AEs were generally mild to moderate and self-limited.

None of the risks seen to date in participants dosed with gepotidacin preclude further clinical development or submission for regulatory approval. 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 intervention (Section 2.3.1). Furthermore, a GSK SRT will monitor safety data instream (see Appendix Section 10.9.6). Careful safety monitoring will also identify any emerging safety issues for gepotidacin and contribute to the benefit-risk profile of gepotidacin.

The investigator may also, at their discretion, discontinue a participant from study intervention at any time and initiate appropriate alternative therapy.

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

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 Objectives and endpoints

Objectives	Endpoints
Primary • To evaluate clinical symptom improvement with gepotidacin treatment in female participants with uUTI at 24 hours (±4 hours).	• Achieving clinical symptom improvement, defined as a decrease from Baseline in CSS total score of at least 1 point at 24 hours (±4 hours), without the need for other systemic antimicrobials.
Secondary • To assess clinical symptom improvement with gepotidacin treatment over time in female participants with uUTI.	• Achieving clinical symptom improvement, defined as a decrease from Baseline of at least 1 point in the CSS total score at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials.
• To assess clinical symptom resolution with gepotidacin treatment over time in female participants with uUTI.	• Achieving clinical symptom resolution, defined as a decrease from Baseline to a CSS total score of 0 at 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials.
• To assess safety and tolerability of gepotidacin treatment in female participants with uUTI.	• Participants with TEAEs, SAEs, and AESIs.
CCI [redacted]	

PRIMARY ESTIMAND:

The primary clinical question of interest is to assess symptom improvement without the need for other systemic antimicrobials in participants at 24 hours (±4 hours) after the initial dose of gepotidacin and having received a second dose of gepotidacin prior to the primary CSS assessment at 24 hours (±4 hours).

The primary estimand is described by the following attributes:

- The population is female participants aged ≥12 years with suspected uUTI, who can adhere to 2 doses of treatment as prescribed.
- The primary endpoint is achieving clinical symptom improvement, defined as a decrease from Baseline in CSS total score of at least 1 point at 24 hours (±4 hours), without the need for other systemic antimicrobials.
- The treatment condition is gepotidacin 1500 mg BID.
- The ICEs and estimand strategies are:
    - Participants unable to take 2 doses as prescribed before the CSS assessment at 24 hours (±4 hours) (Principal Stratum Strategy). Interest lies in the group of participants who complied with the 2 doses as prescribed before the CSS assessment at 24 hours (±4 hours).
    - A participant using other systemic antimicrobials (for uUTI or other infections) on or before the CSS assessment at 24 hours (±4 hours) (Composite Strategy). This ICE is incorporated into the definition of the endpoint.
- The population-level summary to be estimated is percentage of participants who achieve clinical symptom improvement and its 95% Exact Binomial CI.

RATIONALE FOR PRIMARY ESTIMANDS:

- Interest lies in evaluating study intervention benefit through a decrease in CSS total score in participants who achieve 100% compliance to study intervention before the CSS assessment at 24 hours (±4 hours).
- Participants who take other antimicrobials for uUTI indicate lack of treatment benefit and will not be able to achieve symptom improvement (i.e., treatment failures). Participants who take other antimicrobials for other infections might confound the outcome by improving the symptoms. Therefore, such participants are also set to treatment failures.

SUPPLEMENTARY ESTIMAND FOR PRIMARY ENDPOINT:

A supplementary estimand will be considered if CCI participants are not able to comply with the 2 doses as prescribed before the CSS assessment at 24 hours (±4 hours).

The additional clinical question of interest is to assess symptom improvement without the need for other systemic antimicrobials in participants at 24 hours (±4 hours) after the initial dose of gepotidacin.

The supplementary estimand is described by the following attributes:

- The population is female participants aged ≥12 years with suspected uUTI.
- The endpoint is achieving clinical symptom improvement, defined as a decrease from Baseline in CSS total score of at least 1 point at 24 hours (±4 hours), without the need for other systemic antimicrobials.
- The treatment condition is gepotidacin 1500 mg BID.
- The ICEs and estimand strategies are as follows:
    - Participants unable to take 2 doses as prescribed before the CSS assessment at 24 hours (±4 hours) (Treatment Policy Strategy). Interest lies in the treatment effect regardless of compliance with the study intervention.
    - A participant using other systemic antimicrobials (for uUTI or other infections) on or before the CSS assessment at 24 hours (±4 hours) (Composite Strategy). This ICE is incorporated into the definition of the endpoint.
- The population-level summary to be estimated is percentage of participants who achieve clinical symptom improvement and its 95% Exact Binomial CI.

RATIONALE OF SUPPLEMENTARY ESTIMAND FOR PRIMARY ENDPOINT:

- Interest lies in evaluating study intervention benefit through decrease in CSS total score in all participants whether or not compliant with the study intervention.
- Participants who take other antimicrobials for uUTI indicate lack of treatment benefit and will not be able to achieve symptom improvement (i.e., treatment failures). Participants who take other antimicrobials for other infections might confound the outcome by reducing the symptoms. Therefore, such participants are also set to treatment failures.

ESTIMANDS SUPPORTING SECONDARY EFFICACY OBJECTIVES:

The secondary efficacy clinical questions of interest are to assess the following:

- The improvement of clinical signs and symptoms without the need of any other systemic antimicrobials during the 5 days of treatment with gepotidacin in participants who complied with at least 80% of the total prescribed doses before each timepoint.
- The resolution of clinical signs and symptoms without the need of any other systemic antimicrobials during the 5 days of treatment with gepotidacin in participants who complied with at least 80% of the total prescribed doses before each timepoint.

The estimand attributes for the secondary efficacy objectives are as follows:

- The population is female participants aged ≥12 years with suspected uUTI, who can comply with ≥80% doses of treatment as prescribed.

The endpoints are as follows:

- Achieving clinical symptom improvement, defined as a decrease from Baseline of at least 1 point in the CSS total score at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials.
- Achieving clinical symptom resolution, defined as a decrease from Baseline to a CSS total score of 0, at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials.
- The treatment condition is gepotidacin 1500 mg BID.

The ICEs and estimand strategies are as follows:

- Participants unable to take ≥80% doses of gepotidacin up to 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) (Principal Stratum Strategy). Interest lies in the group of participants who complied with ≥80% of the total prescribed doses of gepotidacin up to 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).
- A participant using other systemic antimicrobials (for uUTI or other infections) on or before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) (Composite Strategy). This ICE is incorporated into the definition of the endpoint.
- Study intervention discontinuation (due to any reason) (Treatment Policy Strategy). Interest lies in the treatment effect regardless of study intervention discontinuation.
- The population-level summary to be estimated is percentage of participants who achieve clinical symptom improvement and its 95% Exact Binomial CI.

RATIONALE OF ESTIMANDS SUPPORTING SECONDARY EFFICACY OBJECTIVES:

- Interest lies in evaluating study intervention benefit through decrease in CSS total score in participants who had at least 80% compliance to study intervention up to 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).
- Participants who take other antimicrobials for uUTI on or before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) indicate lack of treatment benefit and will not be able to achieve symptom improvement/resolution (i.e., treatment failures) at the respective time points. Participants who take other antimicrobials for other infections before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) might confound the outcome of the timepoints by reducing the symptoms. Therefore, such participants are also set to treatment failures at the respective time points (Composite Strategy).
- Interest lies in the treatment effect regardless of the 5-day treatment completion, which reflects how participants may be treated in clinical practice. Hence, a treatment policy strategy is appropriate for treatment withdrawal before completing the 5 days of treatment.

SUPPLEMENTARY ESTIMANDS FOR SECONDARY EFFICACY OBJECTIVE:

Supplementary estimands will be considered if [redacted] participants are unable to comply with ≥80% of the total prescribed doses of gepotidacin up to 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).

The additional secondary efficacy clinical questions of interest are to assess the following:

- The improvement of clinical signs and symptoms without the need of any other systemic antimicrobials during the 5 days of treatment with gepotidacin in all participants regardless of compliance with study intervention before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).
- The resolution of clinical signs and symptoms without the need of any other systemic antimicrobials during the 5 days of treatment with gepotidacin in all participants regardless of compliance with study intervention before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).

The estimand attributes for the supplementary estimands for the secondary objectives are as follows:

- The population is female participants aged ≥12 years with suspected uUTI.

The efficacy endpoints are as follows:

- Achieving clinical symptom improvement, defined as a decrease from Baseline of at least 1 point in the CSS total score at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials.
- Achieving clinical symptom resolution, defined as a decrease from Baseline to a CSS total score of 0, at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials.
- The treatment condition is gepotidacin 1500 mg BID.
- The ICEs and estimand strategies are as follows:
    - Participants unable to take ≥80% doses of gepotidacin up to 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) (Treatment Policy Strategy). Interest lies in all participants regardless of compliance with study intervention.
    - A participant using other systemic antimicrobials (for uUTI or other infections) on or before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) (Composite Strategy). This ICE is incorporated into the definition of the endpoint.
    - Study intervention discontinuation (due to any reason) (Treatment Policy Strategy). Interest lies in the treatment effect regardless of study intervention discontinuation.
- The population-level summary to be estimated is percentage of participants who achieve clinical symptom improvement and its 95% Exact Binomial CI.

RATIONALE OF SUPPLEMENTARY ESTIMANDS FOR SECONDARY EFFICACY OBJECTIVES:

- Interest lies in evaluating study intervention benefit through decrease in CSS total score in all participants, whether or not ≥80% compliant with study intervention.
- Participants who take other antimicrobials for uUTI on or before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) indicate lack of treatment benefit and will not be able to achieve symptom improvement/resolution (i.e., treatment failures) at the respective time points. Participants who take other antimicrobials for other infections before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) might confound the outcome of the 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) by reducing the symptoms. Therefore, such participants are also set to treatment failures at the respective time points (Composite Strategy).
- Interest lies in the treatment effect regardless of 5-day treatment completion, which reflects how participants may be treated in clinical practice. Hence, a treatment policy strategy is appropriate for treatment withdrawal before completing 5 days of treatment.

Estimand for secondary safety objective:

The estimand attributes for the secondary safety objectives are as follows:

- The population is female participants aged ≥12 years with suspected uUTI.

The safety endpoints are:

  - TEAEs
  - SAEs
  - AESIs

- The treatment condition is gepotidacin 1500 mg BID.
- The ICE and estimand strategy is as follows:
  - Study treatment discontinuation due to any reason (treatment policy). Interest lies in the group of participants irrespective of whether they completed the study intervention.
- The population-level summary to be estimated are counts and percentages of participants who have experienced TEAEs, SAEs, and AESIs.
- Rationale of estimand supporting secondary safety objectives:
  - The safety endpoints will be captured and reported postdose irrespective of whether or not the participant completed the study intervention.

4. STUDY DESIGN

4.1. Overall design

- Study 219575 is a Phase 3b, open-label, single-arm, multicenter study to evaluate clinical symptom improvement and the safety of gepotidacin during the treatment of uUTIs.
- Female participants ≥12 years of age with 2 or more clinical symptoms of uUTI and nitrite or pyuria from a pretreatment clean-catch midstream urine sample will be offered enrollment into the study and consented/assented (Section 5.1). Participants who meet eligibility requirements will receive gepotidacin 1500 mg administered orally BID for 5 days. (Note: Each dose is to be taken after food consumption and with water to assist with tolerability.)
- Appropriate clinical symptom and safety assessments will be conducted throughout the study. The total duration of study participation is approximately 28 days, with at least 1 planned onsite study visit and 6 telephone call study contacts (see Section 1.3 and Section 8 for study visit details), with allowance for unscheduled visits, as follows:
  - Visit 1 (Baseline/Day 1): onsite
  - Visit 2 (24 hours ±4 hours), Visit 3 (48 hours ±4 hours), Visit 4 (72 hours ±4 hours), and Visit 5 (96 hours ±4 hours): telephone
  - Visit 6 (CCI [redacted]): telephone
  - Visit 7 (Follow-up/Day 28): telephone
  - Unscheduled Visit: onsite or telephone
    - An additional onsite or telephone visit will be arranged if there are safety concerns, lack of response to study intervention, or early withdrawal.
  - Note: Each visit will be assessed over a 24-hour period, starting with the first dose of study intervention received for an individual participant. For example, participants who only receive 1 dose of study intervention on their first calendar day in the study due to a late afternoon/evening Baseline Visit will take the second dose on the following calendar day, which will complete Visit 1. This pattern will continue until all 10 doses are received; thus, the tenth/last dose will be taken prior to Visit 5 (96 hours ±4 hours) (may be 5 or 6 calendar days, depending on when the first dose is taken).
- The study is outsourced and PPD will perform all study-related activities on behalf of GSK. PPD MedCom will perform activities completed by Virtual Research Coordination Center during the study.

- CCI [redacted]

- Refer to Appendix Section 10.11 for details regarding allowed revisions to monitoring due to the coronavirus disease.
- The primary uUTI symptom assessment will be the CSS (Appendix Section 10.1) at Visit 2 (24 hours ±4 hours). Participants must have taken a total of 2 doses of gepotidacin before the Visit 2 (24 hours ±4 hours) assessment of CSS. For the primary endpoint, clinical symptom improvement is defined as a decrease from Baseline of ≥1 point in the CSS total score 24 hours (±4 hours) after starting gepotidacin.
- Other uUTI assessments will include the CCI [redacted] CCI [redacted] (Appendix Section 10.2). CCI [redacted]

A study design schematic is provided in Section 1.2. The SoA is provided in Section 1.3.

Collection of study information via telemedicine during unexpected circumstances will be performed as local regulations permit.

Participant safety will be monitored by the medical monitor, designated safety lead (or delegate), and a GSK SRT throughout the study (Section 8.3.6).

4.2. Scientific rationale for study design

uUTIs affect the quality of life of patients. Feedback from patients and medical providers has demonstrated the need to better assess the burden of UTIs in women and early clinical symptom improvement on a daily basis.

The Phase 3 gepotidacin studies conducted in uUTI (Section 2.2) were conducted based on the need to identify new and effective oral antibiotic treatment options for uUTI, as such therapies are becoming limited due to the increase of MDR uropathogens and ESBL-producing Enterobacterales uropathogens, which are impacting the efficacy of the currently available oral antibacterial treatment options. The studies focused on a primary therapeutic response composite endpoint of both clinical resolution and microbiological eradication, which were measured at specific time points, in line with regulatory guidance [DHHS, 2019].

However, the Phase 3 studies did not measure symptom improvement on a daily basis after the start of study intervention to characterize the time profile of change in clinical symptomatology improvement. The present study will align with the study design and treatment aspects of the gepotidacin Phase 3 studies [Perry, 2022]; however, it will focus primarily on clinical symptom improvement in participants with a uUTI by assessing the CSS on a daily basis after the start of and during gepotidacin treatment. This study data will provide additional clinical data for gepotidacin in uUTIs.

4.3. Justification for dose

The oral gepotidacin dose in this study is 1500 mg BID (total daily dose of 3000 mg) for 5 days. This dosing regimen is the same as evaluated in a Phase 2 uUTI study and the Phase 3 uUTI studies conducted for gepotidacin (Section 2.2) [Perry, 2022]. This dose is justified because it supports the PK attainment targets for gepotidacin against uUTI uropathogens [Scangarella-Oman, 2022] and resulted in achieving noninferiority (Study 204989) and both noninferiority and superiority (Study 212390) results based on therapeutic response at the interim analysis when compared with the nitrofurantoin current first-line agent for efficacious antibacterial treatment of uUTI in women [Gupta, 2011; NICE, 2019; EAU, 2019; Hall, 2023].

4.4. End-of-study definition

A participant is considered to have completed study intervention if the participant has taken all doses of the study intervention (1500 mg BID taken as 2 × 750 mg tablets for a total of 10 doses). A participant is considered to have completed the study if the participant has completed all study visits including Visit 7 (Follow-up/Day 28).

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

5. STUDY POPULATION

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

5.1. Inclusion criteria

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 ICF/IAF and has a body weight ≥40 kg.

   Note: Although participants as young as 12 years of age may enroll in the study, study sites must follow their IRB guidelines. 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 symptoms of uUTI with onset <96 hours prior to study entry: dysuria, frequency, urgency, or lower abdominal pain based on investigator assessment (see Appendix Section 10.1).
3. The participant has nitrite or pyuria (presence of 3+/large leukocyte esterase) from a pretreatment clean-catch midstream urine sample per local laboratory procedures.

Sex

4. The participant is female.

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

- A female participant is eligible to participate if she is a WOCBP who is not pregnant as confirmed by a high sensitivity urine pregnancy test predose at baseline regardless of current or prior contraception use or abstinence, is not breastfeeding, or is not a WOCBP as defined in Appendix Section 10.3.1.2.

  Note: Collection of pregnancy information, contraceptive guidance, and WOCBP definitions are provided in Appendix Section 10.3, and requirements for pregnancy testing during and after study intervention are located in Appendix Section 10.7.

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

Informed consent

5. The participant is capable of giving documented informed consent/assent as described in Appendix Section 10.9.3, which includes compliance with the requirements and restrictions listed in the ICF/IAF and in this protocol.

5.2. 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 intervention, or components thereof, or a history of a drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study 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 in the judgment of the investigator, 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 are to 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

    - Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study intervention (e.g., ileostomy or malabsorption syndrome).
6. The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete study follow-up.

7. The participant has a serious underlying disease that could be imminently life-threatening, or the participant is unlikely to survive for the duration of the study period.

Urinary tract infection/renal/urogenital exclusions

8. The participant has uUTI that is known or suspected to be due to fungal, parasitic, or viral pathogens; or known or suspected to be due to *Pseudomonas aeruginosa* or Enterobacterales (other than *E. coli*) as the contributing pathogen.
9. The participant has symptoms known or suspected to be caused by another disease process, such as overactive bladder, chronic incontinence, or chronic interstitial cystitis, that may interfere with the clinical efficacy assessments or preclude complete resolution of uUTI symptoms.
10. The participant has an anatomical or physiological anomaly that predisposes the participant to UTIs or may be a source of persistent bacterial colonization, including calculi, obstruction or stricture of the urinary tract, primary renal disease (e.g., polycystic renal disease), or neurogenic bladder, or the participant has a history of anatomical or functional abnormalities of the urinary tract (e.g., chronic vesico-ureteral reflux, detrusor insufficiency).
11. The participant has an indwelling catheter, nephrostomy, ureter stent, or other foreign material in the urinary tract.
12. The participant, 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.
13. The participant has known anuria, oliguria, or significant impairment of renal function (creatinine clearance <30 mL/min or clinically significant elevated serum creatinine as determined by the investigator).
14. The participant presents with vaginal discharge at Baseline (e.g., suspected sexually transmitted disease).

Cardiac exclusions

15. The participant has congenital long QT syndrome or known prolongation of the QTc interval.
16. The participant has uncompensated heart failure.
17. The participant has severe left ventricular hypertrophy.
18. The participant has a family history of QT prolongation or sudden death.
19. The participant has a recent history of vasovagal syncope or episodes of symptomatic bradycardia or brady arrhythmia within the last 12 months.
20. The participant is taking QT-prolonging drugs or drugs known to increase the risk of TdP per the ww.crediblemeds.org. “Known Risk of TdP” category at the time of her Baseline Visit, which cannot be safely discontinued from the Baseline Visit (Day 1) through 7 days after the first dose of study intervention; or the participant is taking a strong CYP3A4 inhibitor or a strong P-gp inhibitor.

Cardiac electrocardiogram exclusions

21. The participant has a mean triplicate QTc >450 msec or a mean triplicate QTc >480 msec for participants with bundle-branch block.

    Note:

    - The QTc is the QT interval corrected for heart rate according to QTcB, 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 is to 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.

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

Hepatic exclusions

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

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

Prior antibiotic/antifungal use exclusion

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

Concomitant medication use exclusion

27. The participant plans to use any of the prohibited medications or nondrug therapies from the Baseline Visit through 7 days after the first dose of study intervention as detailed in Section 6.9.

Prior/concurrent clinical study experience

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

5.3. Lifestyle considerations

- Participants will be requested to abstain from sexual activity from the Baseline Visit through 7 days after the first dose of study intervention to prevent possible re-infection.

5.3.1. Meals and dietary restrictions

Study intervention is to be taken after food consumption (a meal or a snack) and with water (see Section 6.1).

5.4. Screen failures

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

Participants who are screen failures are allowed to be rescreened once 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.

5.5. Criteria for temporarily delaying enrollment/randomization/administration of study intervention

Not Applicable.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention (used interchangeably with study treatment) is defined as an investigational product intended to be administered to a participant.

6.1. Study intervention administered

All doses of study intervention are to be taken after food consumption and with water. Participants will receive oral study intervention (gepotidacin [2 × 750 mg tablets]) BID (approximately every 12 hours) for 5 days. Doses are to be taken approximately 12 hours apart, but the allowable window is 6 to 14 hours. There must be at least a 6-hour minimum window between doses. The first oral dose will be administered at the study site at Baseline; participants will self-administer subsequent doses as outpatients thereafter.

Each treatment day will be assessed over a 24-hour period, starting with the first dose of study intervention received for an individual participant. For example, participants who only receive 1 dose of study intervention on their first calendar day in the study due to a late afternoon/evening Visit 1 will take the second dose on the following calendar day, which will complete Day 1. This pattern will continue until all 10 doses are received; thus, the tenth/last dose will be taken prior to Visit 5 (may be 5 or 6 calendar days, depending on when the first dose is taken).

Gepotidacin tablets (750 mg) are not to be broken and must be swallowed whole. The dosage schedule must always encourage study intervention to be taken as close to 12 hours apart as possible.

Table 3 Study intervention administered

Intervention Name	Gepotidacin
Intervention Description	Administer BID (every 12 hours) for 5 days: 1500 mg as 2 × 750 mg tablets for a 3000 mg total daily dose Each dose is to be taken after food consumption and with water
Type	Drug
Dose Formulation	Tablets containing gepotidacin and inactive formulation excipients
Unit Dose Strength	750 mg tablets
Dosage Level	1500 mg BID
Route of Administration	Oral
Use	Investigational
Sourcing	Provided centrally by GSK CCI
Packaging and Labeling	Gepotidacin tablets will be provided in bottles with required labeling
Manufacturer	CCI [redacted]

The supply and shipping of the study intervention will be supported by Xpress.

6.2. Preparation, handling, storage, and accountability

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

6. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
7. 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.

6.3. Assignment to study intervention

This is a nonrandomized, open-label study. All eligible participants will receive oral gepotidacin 1500 mg BID for 5 days.

Study intervention will be dispensed at Baseline.

Returned study intervention is not to be re-dispensed to other participants.

6.4. Blinding

This is an open-label study.

6.5. Study intervention compliance

- When participants are dosed at the study site during the Baseline Visit, they will take their study intervention 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 intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study administration.
- When participants self-administer study intervention as outpatients, compliance with gepotidacin will be assessed through querying the participant during the telephone On-treatment Visits (Visit 2 [24 hours ±4 hours], Visit 3 [48 hours ±4 hours], Visit 4 [72 hours ±4 hours], and Visit 5 [96 hours ±4 hours]) and documented in the source documents and eCRF. In addition, a record of the number of gepotidacin tablets dispensed to and returned by each participant must be maintained and reconciled with study intervention and compliance records. Study intervention start and stop dates, including dates for intervention delays, will also be recorded in the eCRF.

6.6. Dose modification

The study design does not allow for modifications.

6.7. Continued access to study intervention after the end of the study

Participants will not receive any additional treatment from GSK after they discontinue or complete the study. Participants experiencing symptoms suggestive of infection recurrence or relapse at Visit 7 (Follow-up/Day 28) will be assessed and treated per the investigator's judgment.

6.8. 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 is to be instituted, as dictated by the participant's clinical status.

In the event of an overdose, the investigator is to:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention will be interrupted.
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until study intervention can no longer be detected systemically (at least 72 hours), as medically appropriate.
- Obtain a plasma sample for PK analysis within 24 hours from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.9. Prior and 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 is to be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. 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 Section 10.4.

Pain relief use as described in Appendix Section 10.4 is permitted throughout the study. In order to avoid potential masking of pain symptoms, these are permitted if unchanged from predose baseline (i.e., chronic medication). If needed, they are permitted for UTI pain; however, preferably not before Visit 5 (96 hours ±4 hours) to avoid masking. A list of permitted medications commonly used for nausea, vomiting, pain, and diarrhea per investigator discretion is provided in Appendix Section 10.4. Additionally, low dose acetylsalicylic acid (≤100 mg/day) is permitted for the prevention of CV disease events.

A further detailed list of permitted medications is provided in Appendix Section 10.4.

6.9.2. Prohibited medications and nondrug therapies

At the time of enrollment and/or during the study from the Baseline Visit through 7 days after the first dose of study intervention, 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 7 days after the first dose of study intervention.
- 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 through 7 days after the first dose of study intervention. Details regarding website access and additional guidance are provided in Appendix Section 10.4. Of note, ondansetron is not allowed from the Baseline Visit through 7 days after the first dose of study intervention due to its known TdP risk. Alternative antiemetics that are permitted per investigator discretion are listed in Appendix Section 10.4.

  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 Appendix Section 10.4).
- St John's wort or other strong CYP3A4 inducers are not permitted from 14 days before study entry through 7 days after the first dose of study intervention (a list is provided in Appendix Section 10.4).
- Prescription, nonprescription, or supplements that may impact UTI clinical outcomes including, but not limited to, *Uva ursi*, D-mannose, cranberry tablets, phenazopyridine, NSAIDs including ibuprofen and cyclooxygenase-2 inhibitors, and uricosuric drugs (e.g., probenecid and sulfinpyrazone). As described in Appendix Section 10.4, acetylsalicylic acid (doses >100 mg/day) is not permitted.

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

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

The primary reason for premature discontinuation of study intervention will be documented in the eCRF based on the list below:

- Adverse event
- Protocol deviation
- Termination of the study by GSK
- Lost to follow-up
- Investigator discretion
- Lack of efficacy
- Pregnancy
- Study site terminated by sponsor
- Withdrawal by participant
- Participant reached protocol-defined stopping criteria

- Other (specify)
- Death

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

7.1.1. Liver chemistry stopping criteria

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

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

- a participant meets one of the conditions outlined 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 intervention discontinuation is in the best interest of the participant.

Liver safety required actions and follow-up assessments can be found in Appendix Section 10.5.

Figure 2 Phase 3 liver chemistry stopping and increased monitoring algorithm

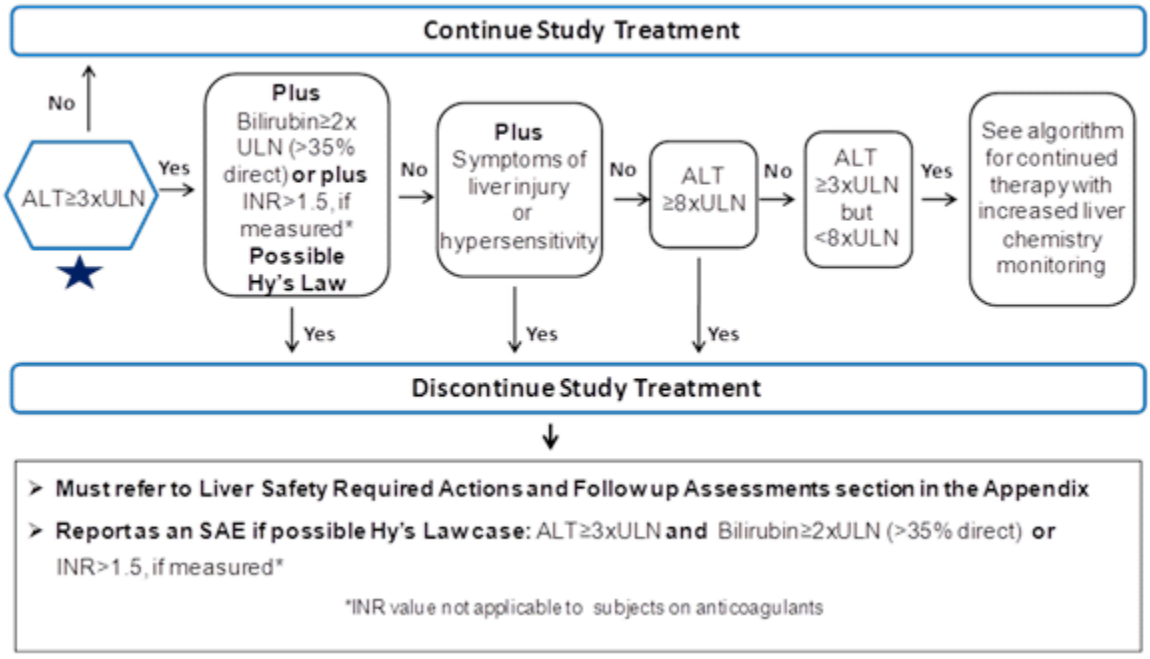
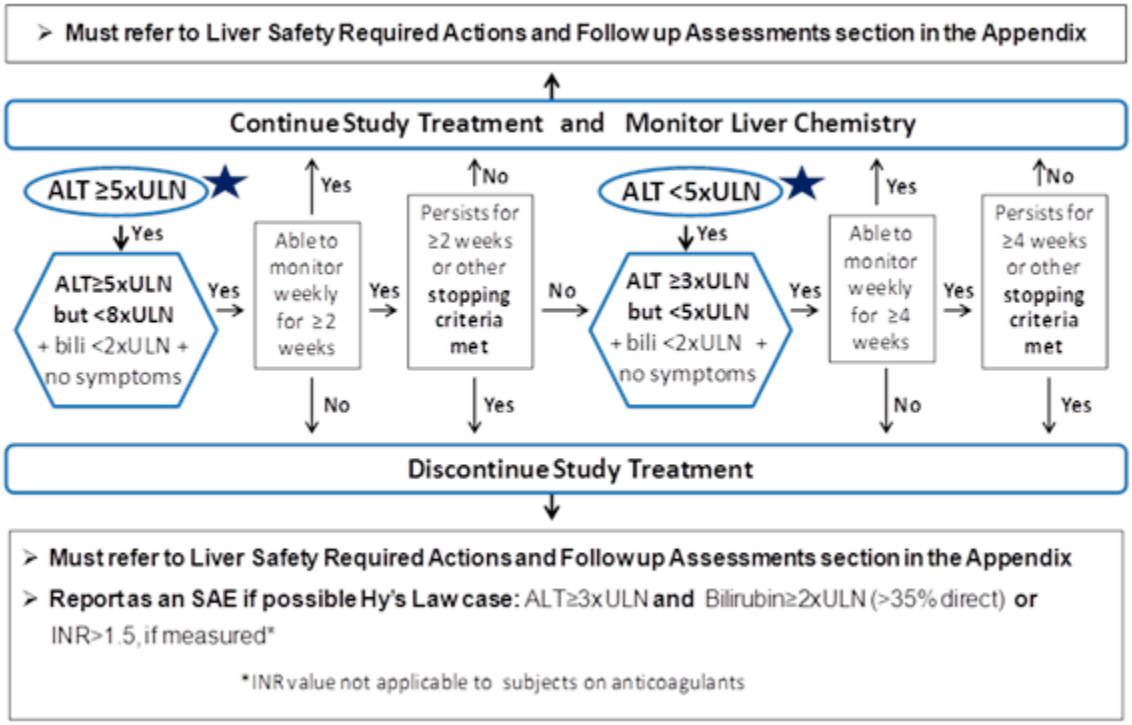


Figure 3 Phase 3 liver chemistry increased monitoring algorithm with continued therapy for ALT ≥3 × ULN but <8 × ULN



7.1.2. QTc stopping criteria

If a clinically significant finding is identified (including, but not limited to, changes from Baseline in QT interval corrected using QTcB or QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding is to be reported as an AE.

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 is to be considered:

- A participant who meets the following bulleted criteria based on triplicate ECG readings will be withdrawn from study intervention:
  - QTc >500 msec OR uncorrected QT >600 msec
  - Change from Baseline of QTc >60 msec
- For 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 are to 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 non-protocol-specified ECGs are an exception.
- The QTc is to be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5- to 10-minute) recording period.

7.1.3. Gastrointestinal evaluation criteria

If a participant meets the criteria in Appendix Section 10.6, *C. difficile* toxin testing will be conducted and the specific eCRF page completed. CDAD is considered an AESI, as described in Section 8.4.4.

7.2. Participant discontinuation/withdrawal from the study

See the SoA (Section 1.3) for procedures to be performed at early withdrawal.

A participant may withdraw from the study at any time at the participant's own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. 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, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/withdrawal from the study will be documented in the eCRF based on the list below:

- Participant lost to follow-up
- Participant withdrew consent
- Termination of the study by GSK
- Investigator discretion
- Other (specify)
- Death

Participants who are withdrawn from the study are to contact the study site and have their clinical symptoms assessed at the time of withdrawal (see the SoA in Section 1.3), if data permit, and return all unused study intervention. 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.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Appendix Section 10.8.5.5).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to participate in 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 participate in a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns are to be discussed with GSK/PPD immediately upon occurrence or awareness to determine if the participant will continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have documented informed consent but are not eligible to proceed will be recorded in the eCRF with a status of "screen failure."
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- Prescreening activities may be conducted, including a prescreening informed consent and urine testing. The required baseline urine specimen may be collected as part of an optional prescreening process, if not already part of standard of care. This specimen can be used for the required baseline procedures of the diagnosis of presumptive uUTI and pregnancy testing.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution, and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- 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 symptoms of uUTI. Participants will be assessed and treated per the investigator's judgment.
- Each visit will be assessed over 24 hours, starting with the first dose of study intervention.
- The study will comprise the following 7 planned visits:
- **Visit 1 (Baseline/Day 1)**: Baseline will be performed onsite as Visit 1. Assessments will be performed as shown in the SoA (Section 1.3), including the following:
    - Participants will provide documented informed consent/assent before any clinical study procedures are performed.

- Demographic data such as year of birth, sex, race, and ethnicity will be recorded in the participant's eCRF. The collection of sex, race, and ethnicity data is necessary to assess and monitor the diversity of the trial participants and to determine if the trial participants are truly representative of the impacted population.
- The participant's medical, uUTI, and surgical history will be obtained by interviewing the participant and/or the participant's LAR and/or by review of the participant's medical records. Any pre-existing conditions or symptoms present prior to the first dose of study intervention will be recorded in the eCRF.
- Participants will provide a pretreatment, clean-catch, midstream urine sample for a urine dipstick test to determine eligibility, as defined in Section 5.1, using their local laboratory.
- The CSS at Visit 1 will be conducted by VRCC via telephone call interview while the participant is onsite prior to the first dose of study intervention as per the SoA (Section 1.3) using the CSS and instructions in Section 8.2.1 and Appendix Section 10.1.The CSS will be reviewed (but not remeasured) by a study physician or otherwise appropriate medically trained staff from the study site onsite along with determination of whether other eligibility criteria are met before the first dose of study medication (Appendix Section 10.1). Only if VRCC cannot do the telephone call, then the study physician or otherwise appropriate medically trained staff from the study site will ask the CSS questions and complete the [redacted] before the first dose of study intervention, therefore only one CSS will be performed at baseline. The same CSS scorer will be used at all other assessment time points (i.e, Visit 1, 2, 3, 4 and 5) for each participant, on all occasions, whenever possible (Appendix Section 10.1). The CSS score will be used to programmatically determine the clinical outcome.
- The [redacted] will be completed (Section 8.2.2 and Appendix Section 10.2) prior to the first dose of study intervention by an appropriately qualified health provider from VRCC.
- Clinical laboratory tests will be conducted, vital signs will be measured, and a 12-lead ECG and physical examination will be performed.
- Following completion of all pretreatment assessments, participants who meet the inclusion and exclusion eligibility criteria will receive oral gepotidacin 1500 mg BID for 5 days. The first dose of study intervention will be administered at the study site under supervision. After dose administration, Visit 1 posttreatment assessments will be performed, as shown in the SoA (Section 1.3). Subsequent to administration of the first dose at the study site, participants will self-administer doses as outpatients, beginning with the second dose. (Note: Each dose is to be taken after food consumption and with water.)
- AEs, SAEs, and concomitant medication use will be recorded, and any AEs or clinically significant changes will be followed accordingly.
- Visit 2 will be scheduled before the participant leaves the study site at Visit 1 (as indicated in Section 1.3).

- **Visit 2 (On-treatment)**: **telephone visit 24±4 h after the first dose**
  - Participants must have taken a total of 2 doses of gepotidacin before the Visit 2 assessment of CSS. This will be confirmed during the Visit 2 telephone call.
  - Clinical symptoms of uUTI will be recorded first based on a participant telephone interview performed by VRCC, who will determine the individual uUTI CSS.
  - The [redacted] will be completed by VRCC last. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.
  - Study intervention compliance will be recorded.
  - Participants will self-administer gepotidacin as an outpatient every 12 hours. Gepotidacin is to be taken after food consumption and with water to assist with tolerability.
  - AEs, SAEs, and concomitant medication use will be recorded, and any AEs or clinically significant changes reported to VRCC during the visit will be followed-up with the study site accordingly.
  - Remind participants of the at home pregnancy test that will be performed before the fifth dose of study intervention.
  - Visit 3 will be scheduled.
- **Visit 3 (On-treatment)**: **telephone visit 48±4 h after the first dose**
  - The CSS assessment will be completed first based on a participant telephone interview performed by VRCC.
  - [redacted]
  - Study intervention compliance will be recorded.
  - Participants will self-administer gepotidacin as an outpatient every 12 hours. Gepotidacin is to be taken after food consumption and with water to assist with tolerability.
  - AEs, SAEs, and concomitant medication use will be recorded, and any AEs or clinically significant changes reported to VRCC during the visit will be followed-up with the study site accordingly.
  - Visit 4 will be scheduled.
- **Visit 4 (On-treatment): telephone visit 72±4 h after the first dose**
  - The CSS assessment will be completed first based on a participant telephone interview performed by VRCC.
  - [redacted]
  - Confirm the result of the at home pregnancy test.
  - Study intervention compliance will be recorded.

- Participants will self-administer gepotidacin as outpatient every 12 hours. Gepotidacin is to be taken after food consumption and with water to assist with tolerability.
- AEs, SAEs, and concomitant medication use will be recorded, and any AEs or clinically significant changes reported to VRCC during the visit will be followed-up with the study site accordingly.
- Visit 5 will be scheduled.

- **Visit 5 (On-treatment): telephone visit 96±4 h after the first dose**
  - The CSS assessment will be completed first based on a participant telephone interview performed by VRCC.
  - The CCI CCI will be completed by VRCC last.
  - Study intervention compliance will be recorded.
  - Participants will self-administer gepotidacin as an outpatient every 12 hours. Gepotidacin is to be taken after food consumption and with water to assist with tolerability.
  - AEs, SAEs, and concomitant medication use will be recorded, and any AEs or clinically significant changes reported to VRCC during the visit will be followed-up with the study site accordingly.
  - After the Visit 5 telephone call, participants will place all study intervention bottles in an envelope provided by the study site and send it back to the study site before Visit 7 (Follow-up/Day 28).
  - Visit 6 will be scheduled.
- **Visit 6: telephone visit CCI after the first dose**

CCI [redacted]

- **Visit 7 (Follow-up/Day 28) Visit: telephone visit 28±3 days after the first dose**
  - The study site will perform this visit. Any AEs, SAEs, and concomitant medication use will be recorded.
- **Unscheduled Visit:**
  - An onsite or telephone Unscheduled Visit may be arranged at any point during the study if there are safety concerns, lack of response to study intervention, or early withdrawal. An alternative antibiotic therapy may be prescribed/administered.

- Clinical symptoms of uUTI will be recorded based on a participant telephone interview performed by a study physician or otherwise appropriately medically trained staff who will determine the individual uUTI CSS.
- The study site will perform this visit. Any AEs, SAEs, and concomitant medication use will be recorded, and any AEs or clinically significant changes will be followed accordingly.

8.1. Administrative procedures

8.1.1. Collection of demographic data

Record demographic data such as date of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race, and ethnicity data is necessary to assess and monitor the diversity of the trial participants and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical history

Obtain the participant's medical history by interviewing the participant/participant's LAR and/or by reviewing the participant's medical records. Record in the eCRF any pre-existing conditions and signs and/or symptoms present prior to the first dose of study intervention including urological or other data pertaining to symptoms which might confound interpretation of urinary symptoms.

8.2. Efficacy assessments

Planned time points for evaluation of clinical symptoms and the measure of clinical efficacy are provided in the SoA.

8.2.1. Clinical symptom score (CSS) and clinical outcomes

Clinical symptoms of uUTI will be recorded based on a participant interview at the time points in the SoA (Section 1.3) using the CSS and instructions in Appendix Section 10.1. At Baseline, the participant must present with at least 2 clinical symptoms of uUTI (i.e., a total CSS ≥2; Section 5.1). Symptom improvement is defined as a ≥1 point decrease in the CSS total score at 24±4 hours.

During Visit 1, the CSS will be conducted by VRCC via telephone call interview while the participant is onsite prior to the first dose of study intervention as per the SoA (Section 1.3) using the CSS and instructions in Section 8.2.1 and Appendix Section 10.1. The CSS will be reviewed (but not remeasured) by a study physician or otherwise appropriate medically trained staff from the study site onsite along with determination of whether other eligibility criteria are met before the first dose of study medication (Appendix Section 10.1). Only if VRCC cannot do the telephone call, then the study site will ask the CSS questions and complete the CCI CCI before the first dose of study intervention. Only one CSS is to be performed at baseline. The same CSS scorer will be

used at all other assessment time points (i.e, visits 2, 3, 4 and 5) for each participant, on all occasions, whenever possible. CSS at visit 6 will be performed by a study physician or otherwise appropriate medically trained staff from the study site (Appendix Section 10.1). The CSS score will be used to programmatically determine the clinical outcome.

Table 4 Clinical improvement and resolution at 24 ±4 hours (Visit 2)

Defining Criteria	Outcome
Resolution of clinical signs and symptoms of uUTI present at Baseline (i.e., reduction of total CSS to 0), without the participant receiving other systemic antimicrobials (not for current uUTI) prior to the 24 ±4 hours (Visit 2) assessment and without receiving other systemic antimicrobials for the current uUTI prior to or 24 ±4 hours (Visit 2).	Clinical resolution
Clinical symptom improvement of at least one point at 24 ±4 hours (Visit 2) from Baseline, without the participant receiving other systemic antimicrobials (not for the current uUTI) prior to the 24 ±4 hours (Visit 2) assessment and without receiving other systemic antimicrobials for the current uUTI prior to or 24 ±4 hours (Visit 2).	Clinical improvement

Table 5 Clinical improvement and resolution at 48 ±4 hours (Visit 3), 72 ±4 hours (Visit 4), 96 ±4 hours (Visit 5), and CCI [redacted] (Visit 6)

Defining Criteria	Outcome
Resolution of clinical signs and symptoms of uUTI present at Baseline (i.e., reduction of total CSS to 0), without the participant receiving other systemic antimicrobials (not for the current uUTI) prior to the assessment at each timepoint and without receiving other systemic antimicrobials for the current uUTI prior to or at each timepoint.	Clinical resolution
Clinical symptom improvement at least one point from Baseline, without the participant receiving other systemic antimicrobials (not for the current uUTI) prior to the assessment at each timepoint and without receiving other systemic antimicrobials for the current uUTI prior to or at each timepoint.	Clinical improvement

CCI [redacted]

8.3. Safety assessments

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

8.3.1. Physical examination

- A physical examination will be performed at the Baseline Visit (Section 1.3).
  - The examination will include assessments of the respiratory, CV, abdominal, gastrointestinal, neurological, and urogenital systems.
  - Height and weight will be measured and BMI calculated and recorded prior to dosing only at the Baseline Visit.
- Investigators are to pay special attention to clinical signs related to previous serious illnesses.
- If an additional physical examination is performed (i.e., Unscheduled Visit), it may be symptom directed, and any clinically significant changes from Baseline or clinically significant new findings will be reported as AEs.

8.3.2. Vital signs

- Vital signs will be measured at the Baseline Visit (Section 1.3).
- Temperature, systolic and diastolic blood pressure, respiratory rate, and pulse rate will be recorded (before blood collection for laboratory tests).
- Vital signs will be measured in a semi-supine position after 5 minutes of rest.
- If an additional vital sign measurements are obtained (i.e., Scheduled/Unscheduled Visit), clinically significant changes from Baseline will be reported as AEs.

8.3.3. 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 7.1.2 for QTc stopping 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, study 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 an additional ECGs are performed (i.e., Scheduled/Unscheduled Visit), clinically significant parameter changes from Baseline will be reported as AEs.

8.3.4. Clinical safety laboratory tests

- Safety laboratory assessments will be performed at PPD Global Clinical Laboratory.
- Clinical safety laboratory tests will be performed at the Baseline Visit (Section 1.3). See Appendix Section 10.7 for the list of clinical laboratory tests to be performed. If additional clinical safety laboratory tests are performed (i.e., Unscheduled Visit), they may be symptom-directed.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring post-treatment during the study as an AE. The laboratory results must be retained with source documents.
- With the exception of the urine dipstick and pregnancy testing, a central laboratory will be used. Any baseline results received while participants are on-treatment that are exclusionary will be assessed by the medical monitor. The medical monitor will contact the investigator and advise on appropriate action with the study intervention.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study are to be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (Section 10.8.1 and Section 10.8.2, respectively).
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology will be identified and the sponsor notified.
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.
- All protocol-required laboratory assessments, as defined in Appendix Section 10.7, must be conducted in accordance with the laboratory manual.

8.3.5. Pregnancy testing

- Pregnancy testing will be performed at the time points listed in the SoA (Section 1.3).
- Female participants of childbearing potential must perform a urine pregnancy test before the administration of any dose of study intervention (Appendix Section 10.7). Pregnancy testing must be done, even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

- An additional pregnancy test using the urine test kit provided by the study site is required to be performed for WOCBP who have not used a highly effective contraception method (Appendix Section 10.3.2) or have not practiced abstinence from penile/vaginal intercourse for at least 14 days prior to the first dose of study intervention. The urine pregnancy kit will be provided to the participant to perform as an outpatient during the defined window (Appendix Section 10.7). A pregnancy test will be performed predose and just before taking the fifth dose. The pregnancy test just before taking the fifth dose will be done at home, with the result confirmed at Visit 4. For any participant with a positive pregnancy test result, study intervention must be immediately discontinued.
- Refer to Appendix Section 10.3.3 for information on study continuation for participants who become pregnant during the study.

8.3.6. Safety monitoring

Participant safety will be monitored by the medical monitor, designated safety lead (or delegate), and a GSK SRT throughout the study. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product. For additional details, see Appendix Section 10.9.6.

8.4. Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information, see Appendix Section 10.8.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or from the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).

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 Section 10.8.

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

All SAEs will be collected from the start of study intervention until Visit 7 (Follow-up/Day 28) at the time points specified in the SoA. However, SAEs assessed as related to study participant (e.g., study intervention, protocol-mandated procedures, invasive tests, or changes in existing therapy) or related to a GSK procedure (non-IMP) will be recorded from the time a participant consents to participant in the study.

All AEs will be collected from the start of study intervention until Visit 7 (Follow-up/Day 28) at the time points specified in the SoA.

Medical occurrences that begin before the start of study intervention but after obtaining documented informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix Section 10.8.5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside the AE/SAE reporting period defined in Section 8.4.1.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. 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 occurrences.

8.4.3. 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 AESIs (as defined in Section 8.4.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix Section 10.8.5.5.

8.4.4. AESIs

Predefined AESIs for this study are CV events, gastrointestinal events, CDAD events, and AEs related to AChE-I (see Section 2.3.1), which will be identified by a prespecified list of coded terms or determined by algorithm, as described in the SAP.

For the CDAD testing procedure and algorithm, see Appendix Section 10.6.

8.4.5. 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.

- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in Appendix Section 10.8.5.3.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

Table 6 Timeframes for submitting SAE, pregnancy, and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hour[a,b]	Electronic AEs Report	24 hour[a]	Electronic AEs Report
Pregnancies	24 hour[a]	Electronic pregnancy notification report	24 hour[a]	Electronic pregnancy follow-up report

a. Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
b. If EDC is unavailable, the site must complete and fax in the paper GSK SAE and Pregnancy Manual Report form. Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.6. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

Details of all pregnancies in female participants will be collected after the start of study intervention and through the follow-up period.

If a pregnancy is reported, the investigator will inform GSK/PPD within 24 hours of learning of the pregnancy and will follow the procedures outlined in Appendix Section 10.3.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.7. Cardiovascular and death events

For any CV events detailed in Appendix Section 10.8.3 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 MedDRA terms. The CV information will 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.

8.4.8. Contact information for reporting SAEs and pregnancies

SAEs and pregnancies must be reported to PPD PVG within 24 hours of learning of the event and to the local IRB/EC per their requirements. All available data must be entered and saved in the eCRF in EDC as soon as it is available within 24 hours of awareness, as it is the primary mechanism of reporting SAE and pregnancy data to GSK. Reference the eCRF Completion Guidelines for additional guidance on completion of the SAE and pregnancy eCRF. Updated SAE and pregnancy data must be submitted within 24 hours of the data being available.

If EDC is unavailable, the site must complete and fax in the paper GSK SAE and Pregnancy Manual Report form to report the event or any follow-up information within 24 hours. Please reference the GSK SAE and Pregnancy. Manual Report form and the investigator instructions that are included within the document.

Table 7 Contact information for reporting SAEs and pregnancies

PPD SAE/Safety Hotline	
Telephone number:	+1 800 201 8725
SAE Fax number:	+1 888 488 9697
Email address:	wilsafety@ppd.com

8.5. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

This section is not applicable.

8.10. Medical resource utilization and health economics

The CCI CCI will be completed at the time points indicated in the SoA (Section 1.3).
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9. STATISTICAL CONSIDERATIONS

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

This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical hypothesis

No formal hypothesis testing will be performed for the primary, secondary, and exploratory endpoints.

9.1.1. Multiplicity adjustment

No multiplicity adjustment will be performed for the primary, secondary, and exploratory endpoints.

9.2. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
ITT	All participants who enrolled in the study (i.e., excluding screen failures).	• Study populations • CCI • Supplementary estimand of the primary objective • Supplementary estimands of the secondary efficacy objectives (Clinical Improvement at 48 hours [±4 hours], 72 hours [±4 hours], 96 hours [±4 hours] and Clinical Resolution at 24 hours [±4 hours], 48 hours [±4 hours], 72 hours [±4 hours], 96 hours [±4 hours]).
Primary Clinically Evaluable at 24 hours (±4 hours)	All participants in the ITT analysis set who were able to adhere to the 2 doses of treatment as prescribed before 24 hours (±4 hours). This is the Primary Analysis Population.	• Estimand for secondary efficacy objectives (Clinical Resolution at 24 hours (±4 hours))
Clinically Evaluable at 48 hours (±4 hours)	All participants in the ITT analysis set who were able to adhere to at least 80% of planned doses of gepotidacin as prescribed up to 48 hours (±4 hours).	• Estimands for secondary efficacy objectives (Clinical Improvement and Clinical Resolution at 48 hours [±4 hours])

Analysis Set	Definition / Criteria	Analyses Evaluated
Clinically Evaluable at 72 hours (±4 hours)	All participants in the ITT analysis set who were able to adhere to at least 80% of planned doses of gepotidacin as prescribed up to 72 hours (±4 hours).	Estimands for secondary efficacy objectives (Clinical Improvement and Clinical Resolution at 72 hours [±4 hours])
Clinically Evaluable at 96 hours (±4 hours)	All participants in the ITT analysis set who were able to adhere to at least 80% of planned doses of gepotidacin as prescribed up to 96 hours (±4 hours).	• Estimands for secondary efficacy objectives (Clinical Improvement and Clinical Resolution at 96 hours [±4 hours]) • CCI [redacted]
Safety	All enrolled participants who received at least 1 dose of study intervention.	• Estimand for secondary safety objective

9.3. Statistical analyses

9.3.1. General considerations/definitions

This study aims to estimate the percentage of participants showing an improvement of the clinical symptoms with gepotidacin treatment in female participants with uUTI.

9.3.2. Primary analysis

The primary analysis will estimate the primary estimand using the Primary Clinically Evaluable at 24 hours (±4 hours) Set.

9.3.2.1. Definition of main analytical approach

Participants who are unable to complete the CSS assessment at 24 hours (±4 hours) will be considered treatment failures and included in the analysis as no improvers. The population-level summary to be estimated is the percentage of participants who achieve clinical symptom improvement along with the 95% Exact Binomial CI.

9.3.2.2. Sensitivity analysis

Participants who are unable to complete the CSS assessment at 24 hours (±4 hours) will be imputed using the MI method. Details of the MI method will be described in the SAP.

9.3.2.3. Supplementary estimand analysis

A supplementary estimand analysis (as described in Section 3) will be considered if CCI [redacted] of participants in the ITT Set are unable to comply with the 2 doses of gepotidacin before 24 hours (±4 hours). The supplementary estimand will be estimated using the ITT Set. Participants who are unable to complete the CSS assessment at 24 hours (±4 hours) will be considered treatment failures and included in the analysis as no improvers. The population-level summary to be estimated is the percentage of participants who achieve clinical symptom improvement along with 95% Exact Binomial CIs for the ITT Set. In the sensitivity analysis, participants who are unable to complete the CSS assessment at 24 hours (±4 hours) will be imputed using the MI method. Details of MI method will be described in the SAP.

9.3.3. Secondary endpoints analyses

Estimands of the secondary efficacy objectives will be estimated using the Clinically Evaluable Sets defined corresponding to each time point, i.e., 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours). The supplementary estimands for the secondary efficacy objectives will be estimated using the ITT Set. Participants who are unable to complete the CSS assessment at a specific time point will be considered treatment failures and included in the summary by time point as no improvers.

The population-level summaries to be estimated are percentage of participants who achieve clinical symptom improvement and clinical symptom resolution at each time point, along with the 95% Exact Binomial CIs.

In each sensitivity analysis, participants who are unable to complete the CSS assessment at a specific time point will be imputed using the MI method. Details of MI method will be described in the SAP.

Safety analyses:

All safety analyses will be performed on the Safety analysis set.

The severity of TEAEs and treatment-emergent SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases DAIDS Table for grading the severity of adult and pediatric AEs (Appendix Section 10.10). All reported TEAEs will be coded using MedDRA and summarized by system organ class and preferred terms.

The safety endpoint will use a Treatment Policy Strategy for the ICE of study intervention discontinuation due to any reason, as safety will be assessed at all postbaseline assessments irrespective of whether the participant completed the study intervention.

The number and percentage of TEAEs, study intervention-related AEs, deaths, SAEs, and AEs leading to study intervention or study withdrawal will be provided.

TEAEs will also be summarized by severity.

The severity of specified TEAEs will be graded according to the DAIDS Table. Data will be tabulated and reported by absolute grade for Grades 3 and higher and shift tables, as appropriate.

AEs of special interest will include CV, gastrointestinal, and CDAD. In addition, TEAEs associated with AChE-I will also be considered special interest.

Potential adverse reactions of gepotidacin will be identified using quantitative methodology if there is sufficient evidence of a causal association with the investigational product (gepotidacin) then qualitative evaluation of the potential adverse reactions will be determined. Further details about adverse reactions will be provided in SAP.

9.3.4. Exploratory endpoints analysis

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[redacted]

9.4. Interim analyses

One or more interim analysis may be conducted to support business need and summarize accumulating data for primary, secondary, and exploratory endpoints as deemed appropriate. Further details will be described in the SAP.

9.5. Sample size determination

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[redacted]

CCI

[redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Clinical symptom score for uUTI

Clinical symptoms of uUTI will be recorded as follows:

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

a. Dysuria is defined as pain or burning when passing urine.

CCI [redacted]

Please note the following clarification points for obtaining this information from participants and score determination during the telephone call interviews:

- Responses to the score criteria will be obtained through direct conversation between the participant and a physician or otherwise appropriately medically trained staff from VRCC who will then determine the actual score based on the clinical symptoms described.
- The CSS at Visit 1 will be conducted by VRCC via telephone call interview while the participant is onsite prior to the first dose of study intervention. The CSS will be reviewed (but not remeasured) by a study physician or otherwise appropriate medically trained staff from the study site onsite along with determination of whether other eligibility criteria are met before the first dose of study medication. Only if VRCC cannot do the telephone call, then the study site will ask the CSS questions and complete the CCI [redacted] CCI [redacted] before the first dose of study intervention. Only one CSS assessment is to be performed at baseline.
- The score criteria will be read out loud verbally to the participant (with verbatim translation into the participant's own language where required). Particularly of note, each score will be specifically dependent and determined based on the participant's normal everyday activities, lifestyle, and background information (e.g., daily fluid consumption, age, past pregnancy history).
- Please ensure to take and record a detailed medical history, including non-uUTI urological symptoms.

CCI [redacted]

CCI

[redacted]

10.3. Appendix 3: Contraceptive and barrier guidance

10.3.1. Definitions

10.3.1.1. Woman of childbearing potential (WOCBP)

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

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty, including breast development and pubic hair growth.

10.3.1.2. Woman of nonchildbearing potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenarchal: Tanner stage 1 (prepubertal)
2. Permanently sterile due to one of the following procedures:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For permanently sterile individuals due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion will be applied to determining study entry. If reproductive status is questionable, additional evaluations are to be considered.

Note: Documentation can come from the site personnel's review of the 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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2. Contraception guidance

- Refer to Appendix Section 10.7 regarding pregnancy testing for female participants at Visit 1 (Baseline) and associated pretreatment contraception and abstinence requirements. Female participants who enter the study using contraception must continue to do so through 7 days after the last dose of study intervention.
- As described in Section 5.3, participants will be requested to abstain from sexual activity from Visit 1 (Baseline) through 7 days after the first dose of study intervention to prevent possible re-infection.

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]

• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception will be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women is to be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Male condom and female condom are not to be used together (due to risk of failure with friction).

10.3.3. 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.
- The initial information will be recorded on the appropriate form and submitted to GSK/PPD within 24 hours of learning of a participant's pregnancy.

- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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 intervention by the investigator, will be reported to GSK/PPD as described in Appendix Section 10.8.5.7. 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 intervention.

10.4. Appendix 4: 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 top-line overview of how to use crediblemeds.org is also provided.

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
Acetaminophen or paracetamol[b]	Pain, fever
Tramadol[b]	Pain
Hydrocodone ER[b]	Pain, severe
Oxycodone[b]	Pain, severe
Loperamide	Diarrhea
Cetirizine	Antihistamine (H_1)
Ebastine	Antihistamine (H_1)
Fexofenadine	Antihistamine (H_1)

Generic Name[a]	**Common Therapeutic Use(s)**
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***

a. Check within each local country to assess if other generic names apply.
b. See Section 6.9.1 for details regarding these medications.
Note: See also Section 5.2 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 6.9.2 for details)	Immunosuppressive therapy
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

a. Check within each local country to assess if other generic names apply.
Note: See also Section 6.9.2 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.

List of strong CYP3A4 inhibitors:

The list below is not exhaustive and is subject to regular updates as new knowledge emerges and new drugs are approved.

Strong Inhibitors	
Amprenavir	Ketoconazole
Atazanavir	Nefazodone
Boceprevir	Nelfinavir
Clarithromycin	Ritonavir
Cobicistat	Saquinavir
Conivaptan	Telaprevir
Fosamprenavir	Telithromycin
Grapefruit juice	Troleandomycin
Indinavir	Voriconazole
Itraconazole	

List of strong CYP3A4 inducers:

Rifampin	Ivosidenib
Mitotane	Phenytoin
Avasimibe	Carbamazepine
Rifapentine	Enzalutamide
Apalutamide	St John's wort extract
Lumacaftor	Phenobarbital

List of prohibited antiretroviral medications:

In general, protease inhibitors and non-nucleoside reverse transcriptase inhibitors used for treatment of HIV or hepatitis C are prohibited.

Table of mechanism of antiretroviral-associated drug-drug-interactions:

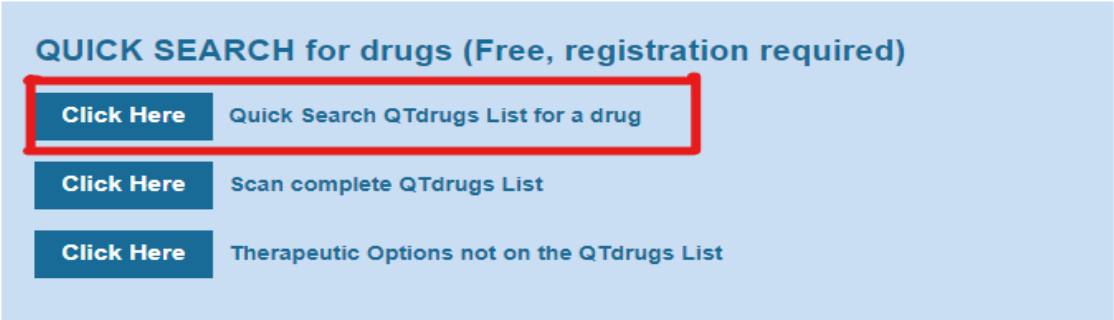
ARV by drug class	**P-glycoprotein**	**CYP450 inhibition**	**CYP450 induction**	**Comments**
PK enhancers				
Cobicistat	Inhibitor	3A4 (2D6)		Used as booster
Ritonavir	Inhibitor	3A4 (2D6)		Used as booster
Protease inhibitors				
Atazanavir	Inhibitor/inducer	3A4		
Darunavir	Inducer	3A4		
Fosamprenavir	Inhibitor	3A4		
Indinavir		3A4		
Lopinavir		3A4		
Saquinavir	Inhibitor	3A4		
Tipranavir	Inducer	(2D6)	3A4	
NNRTIs				
Efavirenz		3A4	3A4	
Etravirine			3A4	
Nevirapine			3A4	

Crediblemeds.org instructions

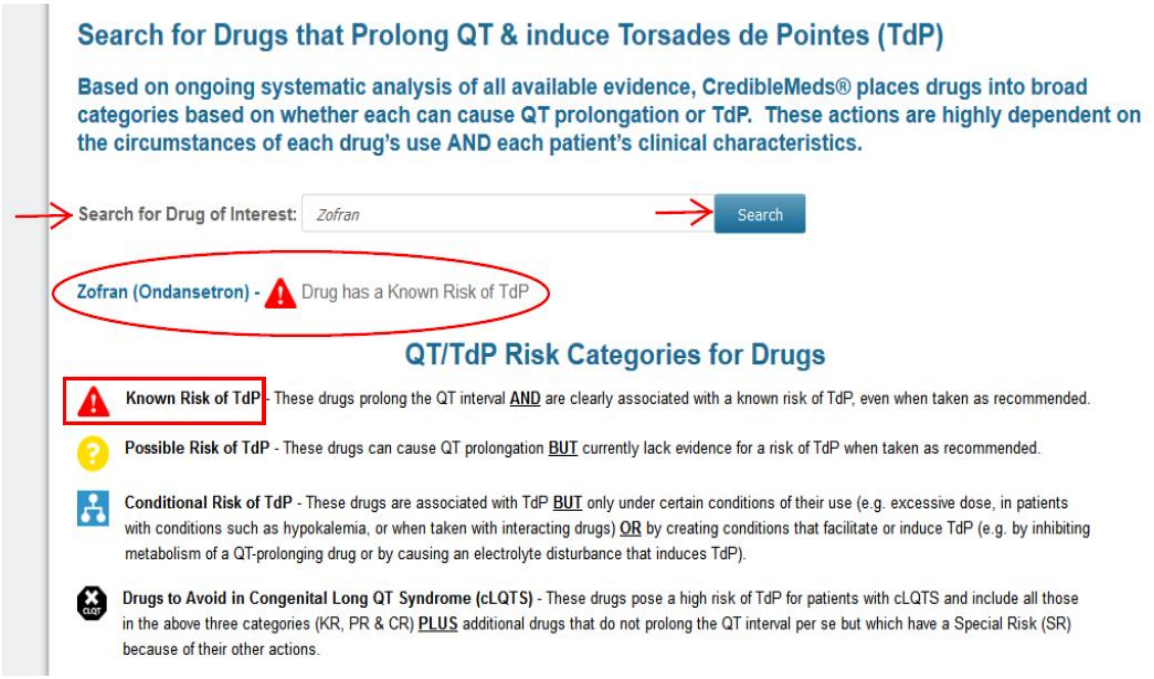
Instructions for accessing www.crediblemeds.org and searching for an exclusionary drug due to its "Known Risk of TdP" category are summarized below.

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 3 search options available. Choose the first option to search for 1 drug at a time. Free registration is required by the website.

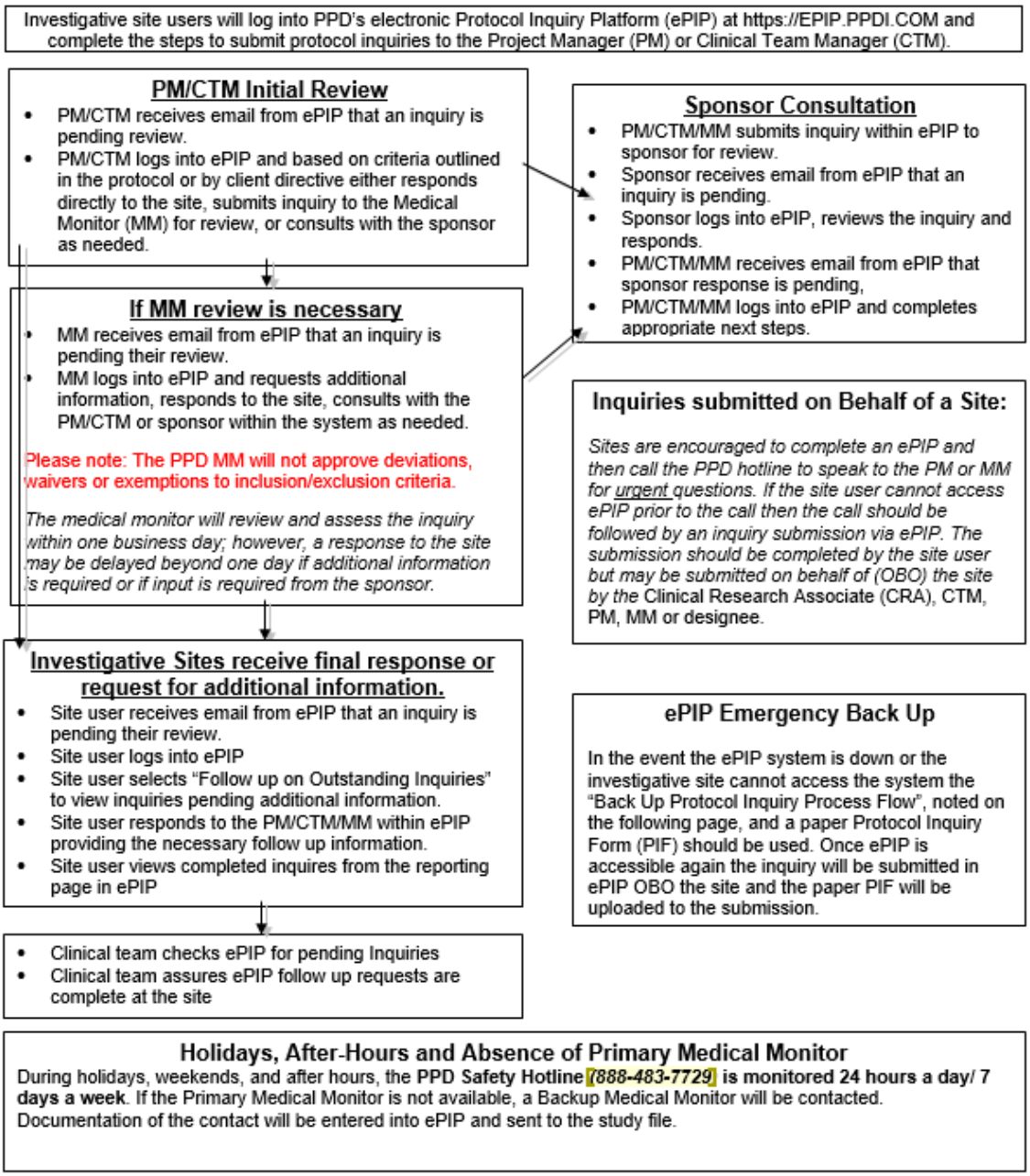


Choosing that option brings you to a screen that allows for you to enter a generic or brand drug name and choose Search. If it has a Known Risk of TdP (i.e., is a prohibited exclusionary medication), it will show a red triangle with an exclamation point as shown here:



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.

ePIP Flow Process



Investigative sites will contact the Project Manager/ Clinical Trial Manager (PM/CTM) with requests for Protocol Inquiries via telephone or fax and complete the Protocol Inquiry Form (PIF):

PM/CTM Telephone Number: EMEA: +45 2215 6855 NA/LA: +1 910 352 6746/+1 760 277 5052 APAC: +886 988 166 395 PM/CTM Fax Number: Bulgaria: 359 24540623 Germany: 49 7212391064 Greece: 302112687245 Hungary: 36 15777339 Mexico: 52 2296903809 Romania: 40 350710208 Spain: 34 935507047 UK: 44 121535710

Project Manager Initial Review

PM/CTM enters the inquiry description into ePIP on behalf of (OBO) the site, attaches the paper PIF, and completes the PM/CTM portion based on protocol criteria or client directive.
PM/CTM consults with the client as needed
PM/CTM determines if MM review is necessary

If MM review is necessary or Direct Site Contact with MM:

- PM/CTM forwards the ePIP to the MM or faxes the paper PIF to the Pharmacovigilance (PVG) Incoming Information Center at: **EMEA/APAC +44 122 337 4102 LA +55 11 3958 0983, NA +1 888 529 3580.**
- MM receives the ePIP or paper PIF
- MM consults with the client and PM as needed and completes the MM portion.
  Please note: The PPD MM will not approve deviations, waivers or exemptions to inclusion/exclusion criteria.
- MM sends the completed ePIP or paper PIF to the Safety Administrator (SA).

The medical monitor will review and assess the inquiry within one business day; however, a response to the site may be delayed beyond one day if additional information is required or if input is required from the sponsor.

If MM review not necessary:

- PM/CTM sends completed PIF to the Investigator
- PM/CTM enters clinically reviewed PIFs into ePIP OBO the site and attaches a copy of the completed paper PIF and complete ePIP workflow.
- PM/CTM files the PIF in the appropriate section of the study file.

- SA sends the completed ePIP or paper PIF to the Investigator and PM
- SA enters medically reviewed paper PIFs into ePIP system On Behalf Of (OBO) the site and attaches a copy of the completed paper PIF.
  - *Note: Paper PIFs entered into ePIP after completion must follow the ePIP workflow through the PM and MM for tracking purposes*

- An electronic copy of the PIF is maintained in ePIP.
- SA sends the paper PIF to the appropriate section of the study file.

- Clinical team checks ePIP for pending PIFs
- Clinical team assures follow up requests are complete at the site

Protocol Inquiry by Phone or Email:

(Only to be used if ePIP or PIF is not an option.)
****Note: sites are encouraged to call the safety hotline to speak to the MM for urgent questions. Calls should be followed by an ePIP submission documenting the question and response for documentation purposes.***

An email or Phone Contact Report (PCR) MUST include the following:

- Client Name/Protocol ID
- Site ID: PI Name and Site #
- Subject ID: Subject # and Initials
- Summarized question being asked by the site or PM
- Summarized resolution of Inquiry

The PM/CTM and SA should be copied on the email.

The SA will submit the inquiry in ePIP OBO the site, attach a copy of the email or PCR, and send the original to the study file.

- *Note: PCRs entered into ePIP must follow the ePIP workflow through the PM and MM for tracking purposes*

Holidays, After-Hours and Absence of Primary Medical Monitor

During holidays, weekends, and after hours, the **PPD Safety Hotline EMEA/APAC +44 122 337 4240; US 888-483-7729; LA +55 11 4504 4801 is monitored 24 hours a day/ 7 days a week**. If the Primary Medical Monitor is not available, a Backup Medical Monitor will be contacted. Documentation of the contact will be sent to the Safety Administrator for tracking and filing.

10.5. Appendix 5: Liver safety: suggested actions and follow-up assessments

Phase 3 liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Phase 3 liver chemistry stopping criteria and required follow-up assessments

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

Required Actions and Follow-up Assessments	
Actions	**Follow-up Assessments**
• Immediately discontinue study intervention • 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 intervention • If restart/rechallenge **not allowed or not granted**, permanently discontinue study intervention and continue participant in the 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**	• Viral hepatitis serology[d] Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) and quantitative hepatitis B DNA • Obtain INR and recheck with each liver chemistry assessment until the transaminase values show downward trend • Obtain blood sample for PK analysis, within 24 hours after last dose[e] • Serum creatine phosphokinase and lactate dehydrogenase • Fractionate bilirubin, if total bilirubin ≥2 × 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

• Monitor participant twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended **For all other criteria:** • 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	remedies, other over-the-counter medications • Record alcohol use on the liver event alcohol intake eCRF page **For bilirubin or INR criteria:** • 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

a. Serum bilirubin fractionation is to be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3 × ULN **and** bilirubin ≥2 × 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 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN **and** INR >1.5, which may indicate severe liver injury (possible 'Hy's Law') **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants.

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).

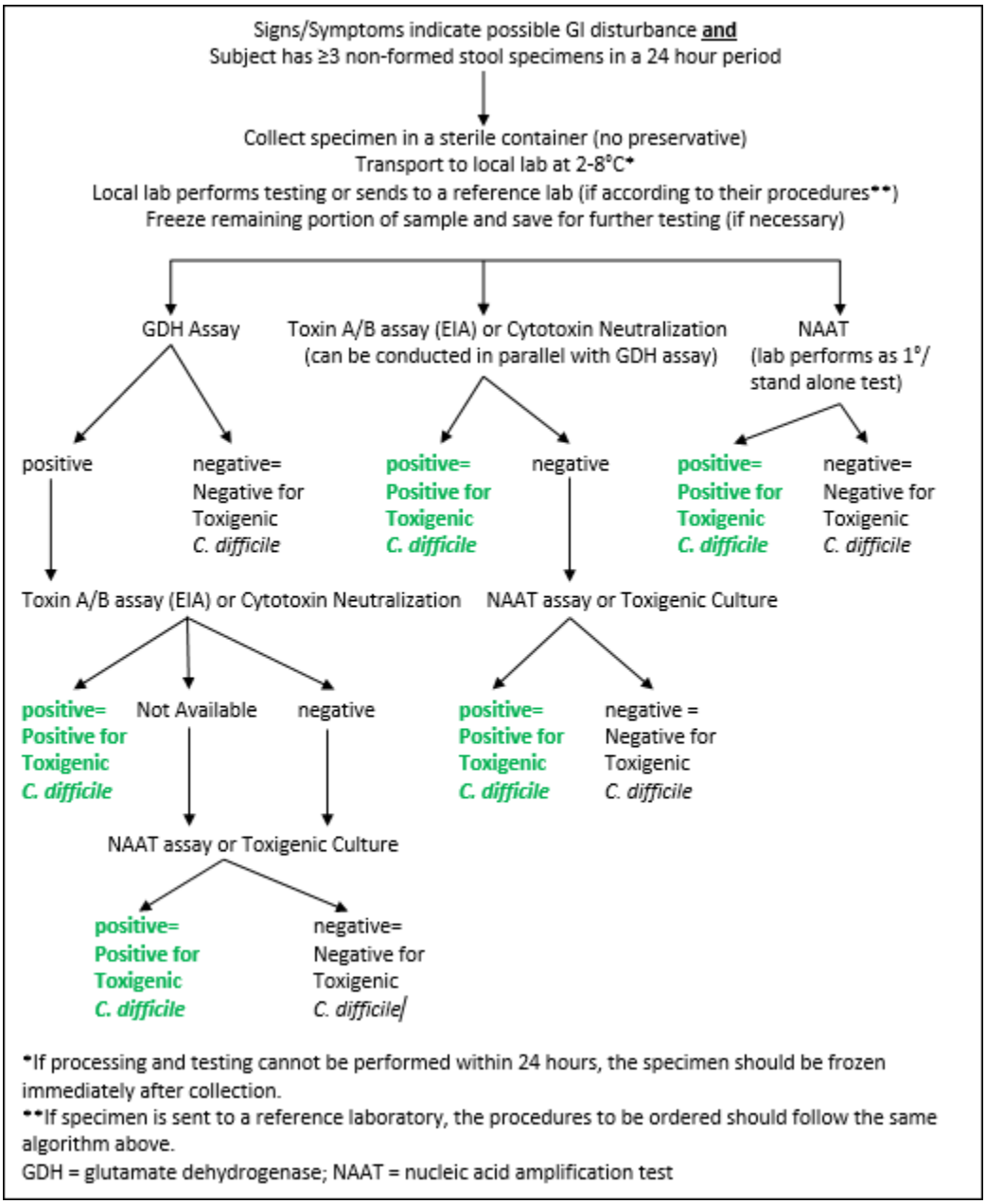
d. Includes: hepatitis A IgM antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

e. PK sample will only be collected for an overdose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention 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 laboratory manual.

Phase 3 liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5 × ULN and <8 × ULN **and** bilirubin <2 × ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3 × ULN and <5 × ULN **and** bilirubin <2 × 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 intervention. • 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 × ULN and <8 × ULN to ≥3 × ULN but <5 × ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3 × ULN and bilirubin <2 × ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

10.6. Appendix 6: CDAD testing procedure, algorithm, and process flow

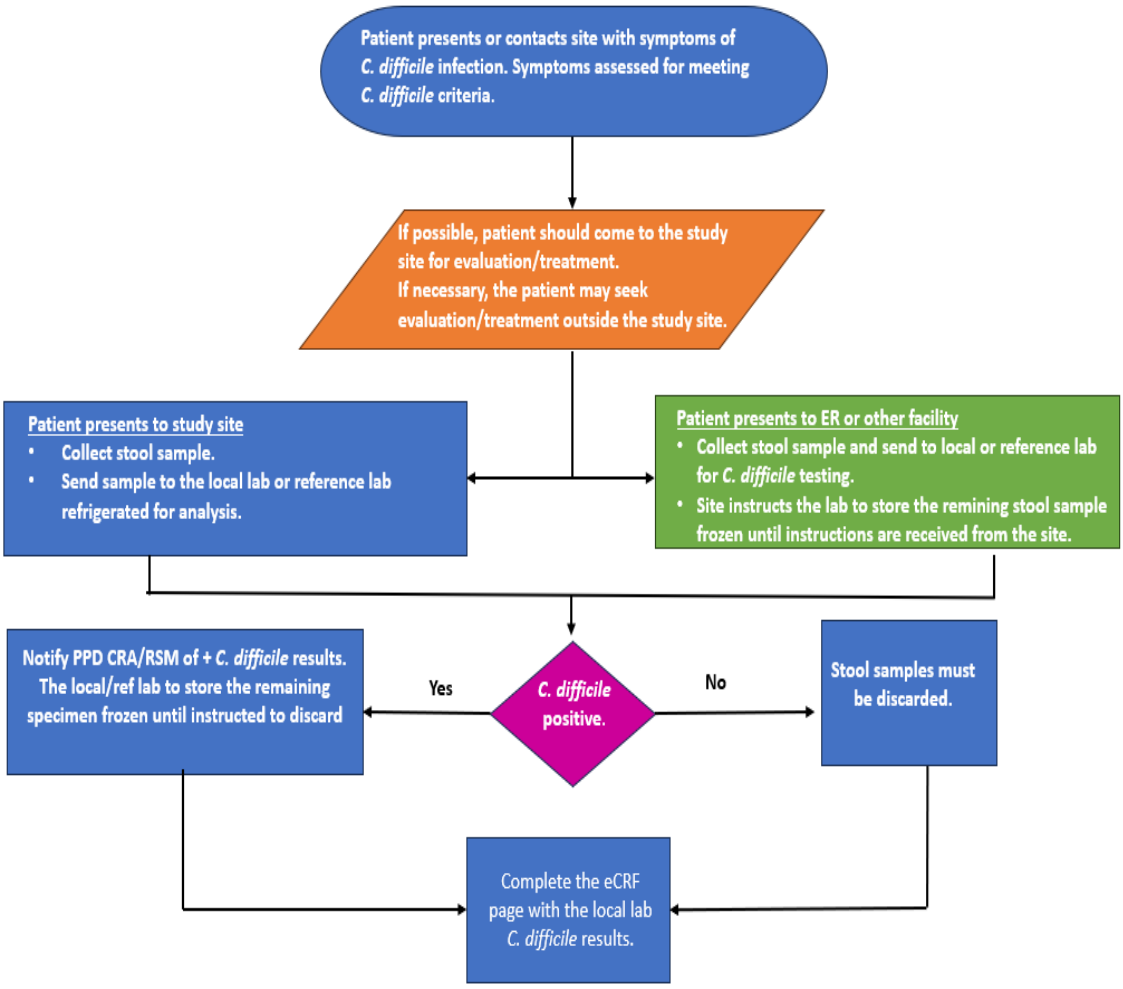


Note: This algorithm is subject to investigator discretion when the clinical presentation and time course of diarrhea (e.g., during or within 12 hours immediately after dosing) do not fit the CDAD definition; consideration is to be given to diarrhea occurring in this early time frame to be suggestive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

Any specimens determined to be positive for toxigenic *C. difficile*:

1. Participant presents/contacts study site with an AE of diarrhea.
2. Symptoms are assessed for meeting *C. difficile* criteria stated above.

3. If symptoms meet the *C. difficile* criteria and the participant presents to the study site and a stool sample is collected and sent refrigerated to the local laboratory for *C. difficile* testing.
4. If the participants present to an emergency room or other (e.g., 24/7 urgent care clinic), the local/reference laboratory will store the remaining sample frozen until advised to discard by the study site.
5. Testing is conducted at the local laboratory for *C. difficile* or a reference laboratory according to their standard testing protocol. Upon completion of testing, the local/reference laboratory will store the remaining sample frozen until advised to discard by the study site.
6. The *C. difficile* eCRF page will need to be completed with the local/reference laboratory *C. difficile* results.



10.7. Appendix 7: Clinical laboratory tests

- The tests detailed in Table 9 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 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Pregnancy testing

- Refer to Section 5.1 for screening pregnancy criteria.
- WOCBP will only be included after a confirmed menstrual period and a negative urine pregnancy test.
- Pregnancy testing will be performed at Visit 1 (Baseline) before study intervention administration. The urine pregnancy test at Baseline will determine study contraception and abstinence requirements as follows:
    - Pregnancy testing at Visit 1 (Baseline) will 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. WOCBP 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 Visit 1 (Baseline).
    - **Note**: ***ONLY*** if the study-specific pregnancy kit provided to the study site is unavailable, a standard urine pregnancy test with a sensitivity of 25 mIU/mL may be used as an exception. A participant with a negative urine pregnancy test result from the standard test may be included in the study ***only*** if the participant has used a highly effective contraception method as described in Section 10.3.2 or has practiced abstinence from penile/vaginal intercourse for at least 14 days before receiving study intervention.
- Before Dose 5, 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 (in Section 10.3.2) or have not practiced abstinence from penile/vaginal intercourse for at least 14 days prior to the first dose of study intervention. 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 intervention must be immediately discontinued.

- 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 participant's participation in the study.

Table 9 Protocol-required clinical safety laboratory tests

Laboratory Tests	Parameters	

Hematology	• Platelet count
	• RBC count
	• Hemoglobin
	• Hematocrit
	• RBC indices:
	  ○ MCV
	  ○ MCH
		• WBC Count With Differential:
		  ○ Neutrophils
		  ○ Lymphocytes
		  ○ Monocytes
		  ○ Eosinophils
		  ○ Basophils

Clinical chemistrya	• Blood urea nitrogen/Urea • Potassium • Creatinine • Sodium • Calcium • Glucose (nonfasting) • Chloride	• AST/SGOT • ALT/SGPT • Alkaline phosphatase • Total bilirubin • Direct bilirubin • Total protein • Magnesium • Phosphorus

Routine urinalysis	• Specific gravity
	• pH, glucose, protein, blood, ketones, nitrite, leukocyte esterase by dipstick
	• Microscopic examination (if blood or protein is abnormal)
	  ○ Epithelial cells
	  ○ RBC
	  ○ WBC
	  ○ Casts
	  ○ Crystals	

Pregnancy testing	• Highly sensitive urine hCG pregnancy test (as needed for WOCBP)[b]	
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in WONCBP only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines)	

NOTES:

a. Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 and Appendix Section 10.4. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT ≥3 × ULN and INR > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to sponsor in 24 hours (excluding studies of hepatic impairment or cirrhosis).

b. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB.

10.8. Appendix 8: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.8.1. Definition of AE

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

Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses will be reported regardless of sequelae. • Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen). • "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 an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.). • 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. Pre-existing diseases will be recorded in the medical history section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before documentation of the informed consent) that did not worsen from baseline.

10.8.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
• Results in death.
• 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.
• Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. 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 is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
• Results in persistent or significant disability/incapacity.

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• Is a congenital anomaly/birth defect in the offspring of a study participant.
• Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
• Other situations: Possible Hy's Law case: ALT ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN (>35% direct bilirubin) or INR >1.5 must be reported as an SAE Medical or scientific judgment will be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events will usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.8.3. Definition of CV events and cases of CDAD

CV definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following CV AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Investigators will be required to fill out a specific CDAD eCRF for CDAD events.

10.8.4. Definition of TEAE

TEAE definition:
A TEAE is an event that emerges during treatment, having been absent pre-treatment, or worsens relative to the pre-treatment state.

10.8.5. Recording, assessment, and follow-up of AEs and SAEs

10.8.5.1. 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 reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK/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.

10.8.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Additional information can be found in Appendix Section 10.10.

10.8.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- 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 their 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.

10.8.5.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only)

10.8.5.5. Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK/PPD within 24 hours of receipt of the information.
- After the initial AE, SAE, or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AESIs (as defined in Section 8.4.4) will be followed until the event is resolved, stabilized, or otherwise explained or until the participant is lost to follow-up.
- Other nonserious AEs or AESIs must be followed until or until the participant is lost to follow-up.

Follow-up during the study

AEs and AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the Follow-up (Day 28) Visit.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the AE report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it will always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in Section 8.4.6.

10.8.5.6. Updating of SAEs, AESIs, and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, AESI, or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information is to be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report is to be sent to the study contact for reporting SAEs or pregnancies (refer to Section 8.4.3).

10.8.5.7. Reporting of SAEs, AESIs, and pregnancies

SAE, AESI and pregnancies Reporting to GSK/PPD via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE, AESI and pregnancies to GSK/PPD will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE, AESI and pregnancies data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE, AESI and pregnancy data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE, AESI and pregnancy from a study participant or receives updated data on a previously reported SAE, AESI or pregnancy after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE, AESI or pregnancy forms (see next section) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any SAEs, nonserious AEs, pregnancy exposure, related to any GSK non-IMP, they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE, AESI and pregnancy reporting can be found in Section 8.4.8.

SAE Reporting to GSK/PPD via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the GSK/PPD medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.8.

10.9. Appendix 9: Regulatory, ethical, and study oversight considerations

10.9.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF/IAF/assent form (if applicable), IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.*
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB*
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures*
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

***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.

10.9.2. Financial disclosure

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

10.9.3. Informed consent/assent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants/participants' LAR and answer all questions regarding the study.
- Potential participants/participants' LAR must be informed that their participation is voluntary. They or their LAR will be required to provide documentation of a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that physical/digital informed consent was obtained before the participant was enrolled in the study and the date the informed consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF/IAF during their participation in the study.
- A copy of the informed consent must be provided to the participant and/or the participant's LAR.
- The investigator must obtain documented assent from the minor participant in addition to the consent provided by the participants' LAR when a minor can assent to participate in a study. The investigator is also accountable for determining a minor's capacity to assent to participation in a research study according to the local laws and regulations.
- In accordance with local laws and regulations, participants who become legally emancipated during the study, i.e., reach the legal age of consent, must be reconsented. The participant must provide consent by signing an ICF, which summarizes the study, includes a consent statement and provides documentation that the participant agrees to continue participating in the study.
- As applicable, the IRB will be consulted before assent form development for guidance around age-appropriate groupings and any specific IRB requirements or local laws for conducting and documenting assent.

Participants who are rescreened are required to sign a new ICF.

In case of unexpected pregnancy, participants must be informed that personal identifiers such as the date of birth and sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.9.4. Study conduct materials and support

Scout Clinical will provide patient reimbursement.

10.9.5. Data protection

- Participants will be assigned a unique identifier. 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.
- GSK will ensure protection of the personal data of the investigator and site staff that is collected within the framework of and for the purpose of the study.
- The participant/participants' LAR must be informed that their/the child's 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/participants'/LAR, that their/their child's data will be used as described in the informed consent.
- The participant/participants' LAR must be informed that their/the child's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.9.6. Committees structure

- A SRT is in place for each GSK product. It comprises a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.9.7. Dissemination of clinical study data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocol summaries prior to study start and target results summaries submission within 12 months of the primary/study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.

- GSK will provide the investigator with the participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.9.8. Data quality assurance

- All participant data relating to the study will be recorded on 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 signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the study to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a different 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.
- When copies of source documents are shared externally for review by a central reader mechanism (e.g., endpoint adjudication committee, expert reader), documents are stored by the external body for 25 years.
- The Electronic Data Capture system will be provided by Medidata Rave.

10.9.9. 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 eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the monitoring guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g., endpoint adjudication committee, expert reader). The non-exhaustive list of documents shared to inform the central reader may include discharge summaries, imaging reports, ECG reports, etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.9.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FPFV (first ICF/IAF signature date) at a country-level.

Study/site termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and is to assure appropriate participant therapy and/or follow-up.

10.9.11. Publication policy

The results of this study may be published in peer-reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.10. Appendix 10: Division of AIDS table for grading the severity of adult and pediatric AEs, version 2.1, July 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [DHHS, 2017] is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term.

The DAIDS Table is available at this link:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as Grade 5.

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Clinical AE NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

10.11. Appendix 11: COVID-19 protocol information specifically for data management and monitoring

- If onsite 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 email approval can be accepted by replying to the relevant email that is sent by GSK/PPD.

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