TITLE PAGE

Protocol Title: A Double-Blind, Double Dummy, Randomized, Phase 1b, Nitrofurantoin Controlled, Repeat Oral Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Microbiological Response of GSK3882347 in Female Participants with Acute Uncomplicated Urinary Tract Infection.

Protocol Number: 212943 Amendment 5

Compound Number: GSK3882347

Brief Title: Safety, tolerability, pharmacokinetic and microbiological investigation of GSK3882347 in female participants with urinary tract infections.

Study Phase: Phase 1b

Sponsor Name and Legal Registered Address:

GSK Research & Development Limited
980 Great West Road
Brentford
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UK

Regulatory Agency Identifying Number(s): [Regulatory Agency identifying number(s) as appropriate]

IND 156644

Approval Date: 10 Jun 2024

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

Sponsor Signatory:

Jennifer Han, MD, MSCE Senior Clinical Development Director, Clinical Lead Clinical Research and Early Programs, Infectious Diseases

Protocol Amendment 5 Investigator Agreement

- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of and will comply with GCP and all applicable regulatory requirements.**
- **That I will comply with the terms of the clinical study site agreement.**
- **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 cooperate with representative(s) of** GSK **in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.**

Study identifier	212943
Approval date	10 Jun 2024
Title	A Double-Blind, Double Dummy, Randomized, Phase 1b, Nitrofurantoin Controlled, Repeat Oral Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Microbiological Response of GSK3882347 in Female Participants with Acute Uncomplicated Urinary Tract Infection
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	Date	Document Identifier
Amendment 5	10 Jun 2024	TMF-19102920
Amendment 4	05 May 2023	TMF-14918563
Amendment 3	07 October 2022	TMF-14918563
Amendment 2	24 February 2022	TMF-14449233
Amendment 1	17 December 2021	TMF-14335823
Original Protocol (00)	20 August 2021	TMF-13952282

Amendment 5 (10 Jun 2024)

Overall Rationale for the Amendment: Changes to overall number of participants randomized, as well as change of one in-person visit to a phone visit to ease site/participant burden.

Section # and Name	**Description of Change**	**Brief Rationale**
CCI [redacted]		
1.1 Synopsis	5 days of dosing intervention has been added.	For clarifying the intervention duration.
1.2 Schema	Pyuria and nitrite have been rewording as pyuria or nitrite	Clarifying urinalysis requirements for inclusion
1.3.2 Schedule of activities: Cohort 2 & 4.1 Overall Design	Removal of Day 4 outpatient clinical visit.	To reduce participant and site burden and improve recruitment, the Day 4 outpatient clinic visit has been removed. All relevant information as specified in the SoA will be collected via a phone call (in the same manner as the phone calls already conducted on Day 3 and Day 5). Specific questions will be asked around any potential

Section # and Name	Description of Change	Brief Rationale
		signs or symptoms of worsening UTI (via the clinical score) or risks for worsening renal function as the in-person blood draw has been removed. Option for conducting urine pregnancy testing on Day 4 will be removed, this should now be conducted on Day 2.
1.3.2. Schedule of activities: Cohort 2	Inclusion of 12-lead ECG on Day 6.	As the Day 4 visit has been changed to a phone call, the ECG that was to be performed on this day will be moved to the next in-person study visit, Day 6.
1.3.2 Schedule of activities: Cohort 2	UTI Clinical Signs and Symptom Score Assessment.	Day 4 visit is being changed from in-person visit to phone call.
1.3.2 Schedule of activities: Cohort 2	Investigators Assessment of Clinical Resolution Response	Day 4 visit is being changed from in-person visit to phone call.
1.3.2 Schedule of activities: Cohort 2	Telephone Call to review clinical symptoms and AEs.	Day 4 visit is being changed from in-person visit to phone call.
1.3.2 Schedule of activities: Cohort 2	In the header, sampling and telephone calls wording has been added and no clinic day has been replaced with Telephone call day.	Clarification that the rows underneath the header include telephone calls on some visits.
1.3.2 Schedule of activities: Cohort 2	In the header, “optional overnight admission permitted” wording has been deleted under "Screening".	The table header text had a typographical error - Cohort 2 remains an outpatient only option for all study participants. Therefore, this text has been removed.
2.3.1 Risk Assessment	Updated wording including additional data generated from nonclinical studies. Removal of “Reproductive toxicity” as a potential risk.	Risk assessment now captures additional data generated from nonclinical studies. “Reproductive toxicity” has been removed as a potential risk. Definitive animal reproductive studies with GSK3882347 have been conducted in rats and rabbits with no hazards identified to date. “Reproductive toxicity” is considered as missing information at this time.

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment of COVID-19	Risk of COVID-19.	This section has been modified to reflect that there is no longer a COVID-19 pandemic, and assessments should be based on community incidence.
4.3 Justification for Dose	Arithmetic mean replaced with geometric means (%CV) from data read out of the Study 212148.	Text states %CV which is now included, and arithmetic mean values updated with geometric mean values which are statistically appropriate for urine concentration and %CV.
5.1 Inclusion criteria	The participant has nitrite OR pyuria (≥10 WBC/mm3 OR >5 WBC/HPF OR the presence of at least 2+ leukocyte esterase) from a pre-treatment clean-catch midstream urine sample based on local laboratory procedures.	Clarified that the leukocyte esterase criteria should be AT LEAST 2+, as 3+ would also qualify.
5.2 Exclusion criteria	Exclusion criteria 11: Updated eGFR range from <90 mL/min/1.73m^2 to <60 mL/min/1.73m^2.	In consultation with the GSK Nephrology Safety Panel and based on the review of non-clinical animal data and blinded data from the ongoing 212943 study (46 participants) and available human PK information obtained from the completed healthy volunteer study (212148), there is sufficient evidence to support widening the eGFR exclusion criteria from the current exclusion of those with eGFR <90ml/min/1.73m^2 to those with eGFR <60ml/min/1.73m^2.
5.2 Exclusion criteria	Exclusion criteria 19 and 20; removed the word “known”.	For clarification.
6.1 Study Intervention Administered	Replaced AM and PM with Dose A and Dose B	While it is ideal for a study participant to start the on-therapy visit in the morning, switching to Dose A and Dose B allows flexibility for study participants that can only start the on-therapy portion of the study in the evening.
6.4 Study Intervention compliance	Removal of bulk supply option	Bulk supply is no longer applicable as the IP is in ready to dispense packaging

Section # and Name	Description of Change	Brief Rationale
8.3.7 Disease Related Events and/or Disease Related Outcomes Not Qualifying as SAEs	Section deleted.	Section removed as not applicable to study. There are no DREs defined for this study nor Disease Related Outcomes that would not qualify as SAEs.
8.3.7 Contact information for reporting SAEs, pregnancies and study holding rules.	Addition of Table 3 summarizing contact information for reporting SAEs, pregnancies and study holding rules.	To reinforce contact information already provided to the study sites and align with protocol template.
8.3.9 Participant Card	New section added	Section added in line with new protocol template as it is applicable to this study. Section reinforces the requirement for study participants to be provided with a "participant card", which is already described in the SRM.
8.9.3 Third Party Vendors	This section has been deleted.	**"The List of Clinical Laboratories and List of key vendors"** is merged into a single separate document outside of the protocol. This provides flexibility to teams to update the list without amending the protocol.
9.2 Analysis Sets	Exposed Population is replaced by Randomized Population and in description 'eligible' word has been removed.	The Exposed Population was renamed to more accurately reflect its definition and to align with new GSK protocol template.

CCI

[redacted]

Section # and Name	Description of Change	Brief Rationale
CCI [redacted]		
10.1.3 Informed consent process	Updates to the master ICF around use of samples for research related and unrelated to this study.	Aligned with the updates to the master ICF template
10.7 Appendix 7: COVID Pandemic Considerations	This section has been deleted.	This Appendix has been deleted as we are no longer in a pandemic so this is not relevant.
11 References	Reference for IB updated. Reference for Prescribing Information for the comparator has been added. Reference for EAU guidelines updated.	An interim update to the investigator brochure was generated. This reference has been added as per new template instructions to avoid copyright infringements. EAU guidelines has been updated and is now dated 2024.
Investigator Agreement	Investigator Agreement page has been added.	To align with new GSK protocol template.
2.2 Background 7.1.1 Liver Chemistry Stopping Criteria 7.2 Participant Discontinuation / Withdrawal from the Clinical Study 8 Study Assessments and Procedures 8,2,4 Clinical Safety Laboratory Tests 8.3.4	Additional changes were made where applicable to align with latest protocol template.	To align with new GSK protocol template (v3.0, 10 January 2024).

Section # and Name	Description of Change	Brief Rationale
Regulatory Reporting Requirements for SAEs 8.3.7 Contact information for reporting SAEs, pregnancies and study holding rules 10.1.3 Informed Consent Process 10.1.4 Data Protection 10.1.5 Committees Structure 10.1.6 Dissemination of Clinical Study Data 10.1.7 Data Quality Assurance 10.2 Clinical Laboratory tests 10.3.1 Definition of AE 10.3.4 Recording, assessment, and follow-up of AE, SAE and pregnancies 10.3.5 Reporting of		

Section # and Name	**Description of Change**	**Brief Rationale**
SAE and pregnancies to GSK 10.10 Abbreviations, Definition of Terms and Trademarks		
Throughout Document	Administrative and editorial changes were made where applicable to align table numbers, formatting, and cross references.	To maintain consistency with template guidance.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Double-Blind, Double-Dummy, Randomized, Phase 1b, Nitrofurantoin Controlled, Repeat Oral Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Microbiological Response of GSK3882347 in Female Participants with Acute Uncomplicated Urinary Tract Infection.

Brief Title: Safety, tolerability, pharmacokinetic and microbiological investigation of GSK3882347 in female participants with urinary tract infections.

Rationale: GSK3882347 is a novel, bacterial attachment inhibitor, designed to treat or prevent uncomplicated urinary tract infections (uUTI) caused by *Escherichia coli* (*E. coli*). GSK3882347 prevents attachment and invasion of the bladder mucosa via inhibition of type 1 fimbrial adhesion, (FimH) protein function on *E. coli*, which cause approximately 70% to75% of all urinary tract infections (UTIs) [Dielubanza, 2011; Barber, 2013, Overcash, 2020, Wagenlehner, 2020]. GSK3882347 binds to the FimH adhesin on type 1 pili of *E. coli*, preventing bacterial adhesion to the bladder mucosal surface by disrupting the interaction between FimH and the mammalian mannose-rich glycoproteins, such as uroplakin Ia and integrins in the bladder. CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

The purpose of this Phase 1b Proof-of-Mechanism (PoM) study is primarily to evaluate the microbiological efficacy of GSK3882347 in females with acute uUTI.

Objectives and Endpoints and Estimands:

Objectives	Endpoints
Primary	
• To assess the microbiological efficacy of GSK3882347 at the Test of Cure (ToC) visit in participants with uUTI who have qualifying *E. coli* at baseline	• Microbiological response at the ToC Visit
Secondary	
• To evaluate the safety and tolerability following CCI [redacted] oral dosing for 5 days of GSK3882347 in participants with uUTI	• Occurrence of adverse events (AEs) and serious adverse events (SAEs) • Clinically significant changes from baseline in laboratory values (hematology, chemistry and urinalysis), vital signs and 12 lead electrocardiogram (ECG) readings
• To evaluate the plasma and urine pharmacokinetic (PK) concentrations following CCI [redacted] oral dosing for 5 days of GSK3882347 in participants with uUTI	Plasma: • GSK3882347 concentration Urine • Urine concentration at 22-24h interval collection post-dose

Objectives	Endpoints
Exploratory*	
CCI [redacted]	
• To evaluate the resolution of clinical symptoms over time of GSK3882347 in participants with uUTI caused by *E. coli*	• Clinical resolution response on Day 2 through to Day 6 (when collected and as data permit), ToC and Follow-up Visit
• To evaluate the resolution of clinical symptoms over time of GSK3882347 in participants with uUTI caused by *E. coli* using an exploratory scoring system	• Clinical symptom score outcome and response on Days 1 through to Day 6 (when collected and as data permit), ToC and Follow-up Visit
CCI [redacted]	

* Details regarding the exploratory analyses will be described in the statistical analysis plan (SAP). Some exploratory data may not be available until after the main database lock and may be analysed/reported separately.

Overall Design:

This Phase 1b study is a double-blind, double-dummy, nitrofurantoin controlled study designed primarily to evaluate microbiological response. Nitrofurantoin will be included in the study to ensure unbiased reporting of safety events. The clinical response CCI [redacted] with GSK3882347 will be evaluated as exploratory endpoints in this study. CCI [redacted]. The study will be separated into 2 cohorts. Cohort 1 will have an inpatient Treatment period and PK analysis will be conducted at frequent timepoints. Cohort 2 will have an outpatient Treatment period and PK analysis will be conducted less frequently, at key trough timepoints.

Brief Summary:

The purpose of this study is to evaluate the safety, tolerability, PK and microbiological response of GSK3882347 capsules in adult female participants with uUTI.

Study details include:

- The study duration will be up to 31 days
- The treatment duration will be up to 5 continuous days
- The visit frequency will be a total of 9 visits in Cohort 1 and 6 visits in Cohort 2.

Number of Participants:

A maximum of 122 participants assuming the evaluability rate observed to date, will be randomly assigned to GSK3882347 or nitrofurantoin in a 3:1 ratio. However, randomization into the study will be stopped when approximately 21 evaluable participants (an evaluable participant is defined as a participant with *E. coli* ($\geq 10^4$ Colony Forming Units [CFU]/mL) confirmed as the causative pathogen for their infection at their baseline assessment are enrolled on to the GSK3882347 CCI [redacted] arm and complete a ToC visit. In the event that the evaluability rate is lower than anticipated CCI [redacted] the maximum number of randomized participants could increase up to 141.

CCI [redacted]

Intervention Groups and Duration: As stated within Number of Participants above with 5 days of dosing intervention.

Data Monitoring/ Other Committee: A GSK Safety Review Team will monitor blinded safety data.

1.2. Schema

Figure 1 Study Schematic for Cohort 1: Full Intensive PK Sampling as Inpatient

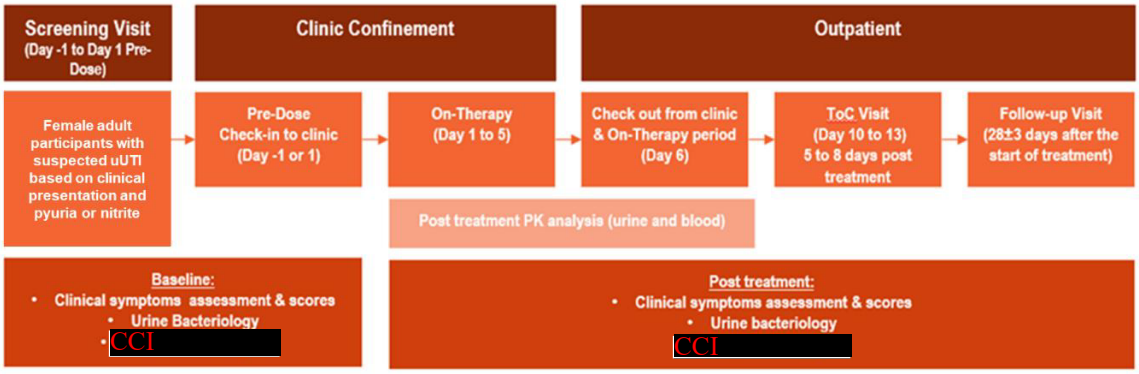
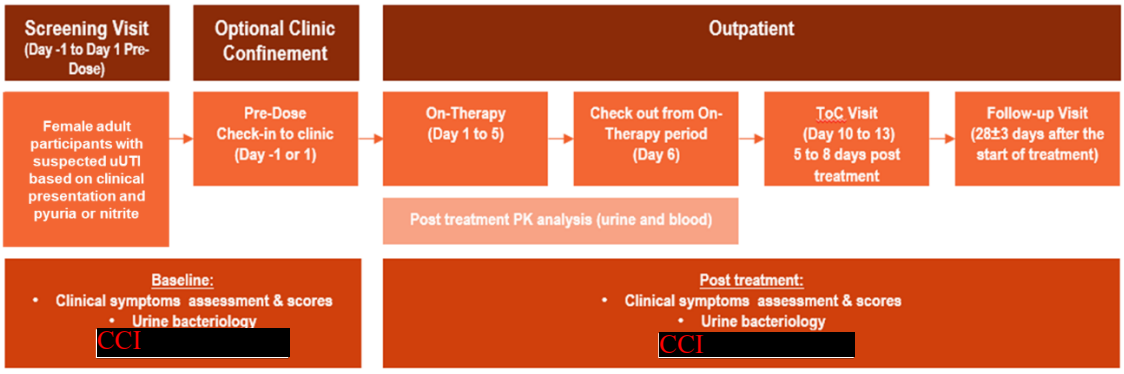


Figure 2 Study Schematic for Cohort 2: Reduced PK Sampling as Outpatient



1.3. Schedule of Activities (SoA)

1.3.1. Cohort 1: Intensive PK Profiling During an Inpatient Intervention Period

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**										Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6				
Informed consent	X											Pre-screen ICF available for local dipstick urinalysis (nitrite and leukocyte esterase) and pregnancy test
Inclusion and exclusion criteria	X	X*										*If required and remaining criteria to confirm.
Demography	X											
Full physical examination	X*								X	X	X	* Height and weight measured only at screening
Medical history (includes substance usage and Family history of premature CV disease)	X											Substances: Drugs, Alcohol Including the number of UTIs participant has had in the last 12 months and within the last 2 years
Urine Drug and Alcohol Observational Assessment	X											

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**										Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6				
COVID test	X*							X	X	X	X	Rapid turnaround tests *Additional parallel polymerase chain reaction (PCR) sample
Urine pregnancy test (for women of child bearing potential)	X^			X*	X*	X*	X*		X	X@		^ Can be completed as a prescreen if Prescreen ICF signed. * One on-therapy test should be conducted either on D2, D3, D4 or D5. @ = If E.D is post Day 6 onward.
Follicle-stimulating hormone and estradiol (as needed for women of non-childbearing potential only)	X											

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**										Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6				
HIV, Hepatitis B and C monitoring sample collection and assessment of history at screening	X											If test otherwise performed within 3 months prior to first dose of study intervention, testing at screening is not required.
Laboratory assessments (haematology, chemistry include liver chemistries and urinalysis)	X*	X		X		X		X	X	X	X	*Sample at screening processed by local labs (Point of Care tests may be utilised when appropriate and are described in Section 10.2)**:** urine dipsticks (nitrite and leukocyte esterase) can be completed as a pre-screen On therapy samples will be obtained pre-dose.
12-lead ECG	X		X			X*			X	X	X	Triplicate ECG for screening, single ECG for all subsequent visits. *Obtained pre-dose

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**										Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6				
Vital signs	X	X	X	X		X		X	X	X	X	Triplicate measurements of blood pressure and pulse rate will be obtained at screening and baseline and averaged. Single measurements will be obtained pre-dose at all other timepoints.
Admission to clinical unit	X*	X										* Can be admitted on the day of screening;
Randomization		X										

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**										Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6				
Genetic blood sample (optional)		X										Pre-dose (baseline), Germline genetic research may be described in a separate ICF or as part of a combined informed consent form (ICF). A separate signature is required where participantparticipation is optional. This sample differs from urine bacterial samples that will be collected for potential genetic analysis.
Study intervention administration			X	X	X	X	X					

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**									Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6				
AE review			←==========							X	X	Record AE from time of first dose of study Treatment. Stool sample collected and tested if the Investigator suspects *Clostridioides difficile (C. difficile)* infection during the study. For CV related events see Section 8.3.6
SAE review	X	X	←==========							X	X	Record SAE from time informed consent signed.
Concomitant medication review		X	←==========→*							X	X	*Including any rescue medication (Section 6.8.3)
UTI Clinical Symptom Score Assessment	X	X*		X	X	X	X	X	X	X	X	*Considered screening and Pre-dose baseline assessment if screening visit is on Day 1. The same personnel should make the assessment for the participant throughout the study, where possible.

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**										Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6				
Investigators Assessment of Clinical Resolution Response				X	X	X	X	X	X	X	X	The same Investigator should make the assessment for the participant throughout the study, where possible.
PK Urine samples		X	X*	X	X	X	X*			X+		*Serial PK; see detailed PK Table Section 1.3.1.1 + If Study Intervention is discontinued on Day 1 to Day 5, collect samples per protocol for corresponding day on Table Section 1.3.1.1 for the last PK collection(s).

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**										Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6				
Urine Microbiology Bacterial sample		X@		X*	X*	X*	X*	X@	X@	X	X	Clean-catch midstream urine sample sent to central labs CCI [redacted] *Pre-dose CCI [redacted]
PK Plasma samples		X	X*	X	X	X	X*	X		X+		*Serial PK; see detailed PK Table Section 1.3.1.2 + If Study Intervention is discontinued on Day 1 to Day 5, collect samples per protocol corresponding day on Table Section 1.3.1.2 as the last PK collection(s).

Cohort 1: Intensive PK Procedure	Screening # (Day -1, can be on Day 1)	**Cohort 1: Intensive PK & Clinic Visits [Days]**											Notes: # E-consent may be used. ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Clinic Constrained Intervention Period [Days]								**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3	4	5	6					
CCI [redacted]													
Meals		X	X	X	X	X	X	X					
Daily fluids		X	X	X	X	X	X	X					
Discharged from clinical unit								X					

A site may use an electronic method to obtain participant signature as long as it conforms to 21CFR part 11 and is approved by IRB

1. Baseline data will be collected at pre-dose on Day 1 (except for triplicate ECG which uses Day -1 screening)
2. All screening activities to occur within 24 hrs of dosing. Local Lab results may be extended 24+6hrs as long as report assessed prior to dosing.
3. The 24 hour screening period starts from the signing of the main ICF.
4. Point of Care tests may be utilized when appropriate and describe in Section 10.2 for day -1 screening visit and only on prior agreement with GSK

1.3.1.1. Cohort 1 Detailed Urine PK Sampling

VISIT DAY	Cohort 1: Intensive PK: Urine									
	Intervals: Hours (h)[1]									
	Pre-dose	0-2h	2-4h	4-6h	6-8h	8-10h	10-12h	12-22h	22-24h	Notes
Day 1	X	X	X	X	X	X	X	X	X	Participants will void bladder prior to dosing and this predose urine sample will be retained as a control (not combined with 0-2hr urine collection).
Day 2									X	22-24 hours post – Day 2 dose
Day 3									X	22-24 hours post – Day 3 dose
Day 4									X	22-24 hours post – Day 4 dose
Day 5		X	X	X	X	X	X	X	X	22- 24 hours post – Day 5 dose

1. The weight of each urine collection will be accurately measured and recorded at the end of each interval prior to aliquoting.
2. Baseline data will be collected at pre dose on Day 1 (except for triplicate ECG which uses Day -1 screening)

1.3.1.2. Cohort 1 Detailed Plasma PK Sampling

VISIT DAY	Cohort 1: Intensive PK: Plasma											
	Hours (h)											
	Pre-dose	0.25h	0.5h	1h	1.5h	2h	4h	6h	8h	12h	16h	Notes
Day 1	X	X	X	X	X	X	X	X	X	X	X	
Day 2	X											24 hours post – Day 1 dose
Day 3	X											24 hours post – Day 2 dose
Day 4	X											24 hours post – Day 3 dose
Day 5	X	X	X	X	X	X	X	X	X	X	X	
Day 6	X											24 hours post – Day 5 dose

1.3.2. Cohort 2 Reduced PK Sampling During an Outpatient Intervention Period

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]**										Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Outpatient Clinic intervention Period [Days] *= Telephone call day							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6				
Informed consent	X											Prescreen ICF available for local urinalysis dipstick (nitrite and leukocyte esterase) and pregnancy test
Inclusion and exclusion criteria	X	X*										*If required and remaining criteria to confirm.
Demography	X											

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]**										Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Outpatient Clinic intervention Period [Days] *= Telephone call day							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6				
Full physical examination	X*								X	X	X	* Height and weight measured only at screening
Medical history (includes substance usage and Family history of premature CV disease)	X											Substances: Drugs, Alcohol Including the number of UTIs participant has had in the last 12 months and within the last 2 years
Urine Drug, Alcohol Observational Assessment	X											
Past and current medical conditions	X											Including the number of UTIs participant has had in the last 12 months and within the last 2 years
COVID-19 test	X		X[#]	X[#]				X[#]	X	X	X	Rapid turnaround tests # Additional rapid turnaround test if required by local sites.

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]**										Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Outpatient Clinic intervention Period [Days] *= Telephone call day							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6				
Urine pregnancy test (for women of child bearing potential)	X^			X*					X	X@		^ Can be completed as a prescreen if Prescreen ICF signed. * One on-therapy test should be conducted on D2 @ = If E.D is post Day 6 onward.
Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)	X											
HIV, Hepatitis B and C monitoring sample collection and assessment of history at screening	X											If test otherwise performed within 3 months prior to first dose of study intervention, monitoring sample at screening is not required.

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]**										Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Outpatient Clinic intervention Period [Days] *= Telephone call day							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6				
Laboratory assessments (haematology, chemistry include liver chemistries and urinalysis)	X*	X		X				X	X	X	X	*Sample at screening processed by local labs: urine dipsticks (nitrite and leukocyte esterase) can be completed as a prescreen On therapy samples will be obtained pre-dose. See footnote
12-lead ECG	X		X					X	X	X	X	Triplicate ECG at screening and single ECG at all subsequent visits.
Vital signs	X	X	X	X				X	X	X	X	Triplicate measurements of blood pressure and pulse rate will be obtained at screening and baseline and averaged. Single measurements will be obtained pre-dose at all other timepoints.
Randomization		X										

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]**										Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Outpatient Clinic intervention Period [Days] *= Telephone call day							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6				
Genetic sample (optional)		X										Pre-dose (baseline), Germline genetic research may be described in a separate ICF or as part of a combined ICF. A separate signature is required where participant participation is optional. This sample differs from urine bacterial samples that will be collected for potential genetic analysis.
Study intervention administration			X	X	X*	X*	X*					* Supplies for home administration, supplied at previous site visit; patients may also be sent home with PM dose on clinic days
Patient Diary Distribution and Review			X	X*		X*		X*				Paper diaries to record date and time medication taken and conmeds *Review and record diary entries in in electronic case report form (eCRF) (Day 6 is review only)

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]**									Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Outpatient Clinic intervention Period [Days] *= Telephone call day							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6				
AE review			←==========					==========→		X	X	Record AE from time of first dose of study Treatment. Stool sample collected and tested if the Investigator suspects *Clostridioides difficile (C. difficile)* infection during the study. For CV related events see Section 8.3.6
SAE review	X	X	←==========					==========→		X	X	Record SAE from time informed consent signed.
Concomitant medication review		X	←==========					==========→ *		X	X	*Including any rescue medication (Section 6.8.3.)

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]** **Outpatient Clinic intervention Period [Days] *= Telephone call day** 1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6		**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
UTI Clinical Signs and Symptom Score Assessment	X	X[#]		X		X*		X		X	X	X	#Considered screening and Pre-dose baseline assessment if screening visit is on Day 1. The same personnel should make the assessment for the participant throughout the study, where possible. *Assessment of the UTI clinical signs and symptoms score must be conducted via telephone. The investigator should also assess for any nausea, vomiting, diarrhea or poor fluid intake that may pose a potential risk to renal function.
Investigators Assessment of Clinical Resolution Response				X		X*		X		X	X	X	The same Investigator(s) should make the assessment for the participant throughout the study, where possible. *The Investigators Assessment of Clinical Resolution Response must be conducted via telephone.

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]**										Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
		Outpatient Clinic intervention Period [Days] *= Telephone call day							**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	
		1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6				
Telephone Call to review clinical symptoms and AEs					X	X	X					If contact cannot be made, 3 separate attempts should be made to speak with the participant. .
PK Urine sample				X*				X*		X^{+}		*= Pre dose, 24h after previous dose Participants will void bladder prior to dosing. Sample will be accurately weighed and recorded prior to aliquoting. + If Study Intervention is discontinued no samples will be collected at subsequent visits.

Cohort 2: Reduced PK Procedure	Screening # (Day -1 or can be on Day 1)	**Cohort 2: Reduced PK Sampling & Clinic Visits and Telephone calls [Days]** **Outpatient Clinic intervention Period [Days] *= Telephone call day** 1 (Pre-Dose)	1 (Post-Dose)	2	3*	4*	5*	6	[redacted]	**ToC** (D10 to D13) 5 to 8 days post treatment	**E.D.^**	**Follow-Up** (28 ±3 days following first dose)	Notes: # E-consent may be used ^E.D = early discontinuation/withdrawal; see early discontinuation section
Urine Microbiology Bacterial sample		X@		X*				X@		X@	X	X	Clean-catch midstream urine sample sent to central labs CCI [redacted] *Pre-dose CCI [redacted]
PK Plasma sample				X*				X*			X+		*= Pre dose, 24h after previous dose + If Study Intervention is discontinued no samples will be collected at subsequent visits.

CCI [redacted]

- The Competent Authority (CA) and independent ethics committee (IEC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the IEC before implementation.
- # A site may use an electronic method to obtain participant signature as long as it conforms to 21CFR part 11 and is approved by IRB: Baseline data will be collected at pre dose on Day 1 (except for triplicate ECG which uses Day -1 screening)
- All screening activities to occur with 24 hrs of dosing. Lab results may be extended 24 +6 hrs as long as report assessed prior to dosing.
- The 24 hour screening period starts from the signing of the main ICF.
- Point of Care tests may be utilized when appropriate and describe in Section 10.2 for day -1 screening visit and only on prior agreement with GSK

2. INTRODUCTION

2.1. Study Rationale

GSK3882347 is a novel, bacterial attachment inhibitor, designed to treat or prevent uncomplicated urinary tract infections (uUTI) caused by *Escherichia coli* (*E. coli*). During an acute uUTI, *E. coli* binds and enters bladder mucosa cells via the bacterial FimH-containing pili. Within the uroepithelial cells the bacteria rapidly divide and are subsequently released from the mucosal cells into the bladder prompting further cycles of attachment, invasion and replication. When used for the treatment of acute bacterial infection, as is proposed in this Phase 1b study, it is anticipated that GSK3882347 will be present in the urine of study participants at sufficiently high concentrations to prevent binding of the *E. coli* which are released into the bladder during these replicative bursts, thus halting further infection cycles and leading to microbiological and clinical resolution of disease. [Flores-Mireles, 2015].

2.2. Background

GSK3882347 binds to the FimH adhesin on type 1 pili of *E. coli*, preventing bacterial adhesion to the bladder mucosal surface by disrupting the interaction between FimH and the mammalian mannose-rich glycoproteins, such as uroplakin Ia and integrins in the bladder. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

For Macrobid (Control Active comparator), detailed description of pharmacology, efficacy and safety are provided in the current [Macrobid Prescribing Information, 2024].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of GSK3882347 and Nitrofurantoin may be found in the Investigator's Brochure [CCI [redacted]] and the locally approved prescribing information (Summary Product Characteristics), respectively.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: GSK3882347		
Key potential risk:		
Gastrointestinal toxicity (including body weight loss, decreased food consumption and dehydration), for awareness.	**Nonclinical** In a 14-day definitive toxicity study, dogs given ≥CCI mg/kg/day had severe body weight loss, decreased food consumption, dehydration, emesis and abnormal feces. Dogs given CCI mg/kg/day were euthanized early due to severity of body weight loss. Pregnant rabbits given ≥CCI mg/kg/day had severe body weight loss and decreased food consumption after 1 to 2 weeks of daily dosing, which resulted in early euthanasia and 1 early death at CCI mg/kg/day. These changes in dogs and rabbits resulted in early euthanasia or death at the doses stated. In a 13 week toxicity study in dogs, doses up to CCI mg/kg/day were tolerated with non-adverse signs of salivation and emesis throughout the dosing period.	Dosing for a maximum of 5 days. Standard clinical monitoring with elicitation of clinical symptoms; physical examinations and routine safety blood haematology and chemistry tests (Section 1.3). Monitoring for AEs. Any GI event will be monitored and recorded for severity according to DMID (division of microbiology and infectious diseases) adult toxicity guidance (Section 10.7).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical During the first time in human (FTIH) (212148) study in healthy participants, there were no reports of any gastrointestinal serious adverse events. There were two non-serious gastrointestinal AEs reported that were considered related to study treatment (mild intermittent diarrhoea in 2 participants). One participant received placebo and one received GSK3882347 CCI mg CCI for 7 days. In both cases the diarrhea was mild in severity and recovered within 48 hours.	
Renal Changes	**Nonclinical** Dogs given ≥CCI mg/kg/day for 14 days had minimal to slight degeneration/ regeneration with changes in clinical pathology parameters (increased serum urea nitrogen and creatinine) which also correlated with clinical signs of dehydration as these dose levels were not considered tolerated. In a 14-day CCI toxicity study in rats, minimal to moderate tubule cell hypertrophy was noted in the kidney of animals given ≥CCI mg /kg /day, slight tubule cell degeneration /necrosis of tubule cells was also noted in one	Dosing at a lower dose and for shorter duration than the regimen used in the FTIH study CCI mg CCI for a maximum of 5 days). Standard clinical monitoring with elicitation of clinical symptoms; physical examinations and routine safety blood haematology, chemistry tests and urinalysis (Section 1.3). Monitoring for AEs. Any renal event will be monitored and recorded for severity according to DMID (division of microbiology and infectious diseases) adult toxicity guidance (Section 10.7). Monitoring of serum creatinine levels with follow up assessments obtained for any change from baseline >1.5X (Section 8.2.4.2)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	male given CCI mg /kg /day. In the urinary bladder epithelial cell hypertrophy was noted in animals given ≥CCI mg/kg/day. These renal and bladder findings were not accompanied by changes in clinical pathology or alterations of urinalysis endpoints. In a 14-day BID CCI investigative study in rats, minimal to moderate tubular degeneration/regeneration was seen in rats given ≥CCI mg/kg/day twice daily (total daily dose ≥CCI mg/kg/day) which survived for the duration of the study, along with multifocal proximal tubule and/or collecting duct hyaline droplets, minimal to mild/slight multifocal medullary collecting duct hypertrophy and minimal to slight hypertrophy in the bladder. There were also decreases in serum chloride and potassium but no changes in urea or creatinine. In a 13-week toxicity study, 5 rats given CCI mg/kg/day were euthanized in moribund condition between Days 26 and 88 (with body weight loss and clinical signs of non-tolerability including dehydration) following CCI administration of GSK3882347. The clinical condition was attributed to tubular	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	degeneration/ regeneration in the kidney. Other urinary tract findings included tubular dilatation, interstitial mononuclear cell infiltration, neutrophilic inflammation in the papilla and epithelial and urothelial hypertrophy/ hyperplasia of the papilla lining, pelvis and/or urinary bladder, respectively. In addition, there were increases in serum urea, creatinine, phosphorus and potassium and increased urinary protein and glucose excretion in rats given CCI mg/kg/day. In a 26-week rat toxicity study, there was a slight increased incidence of tubule basophilia (graded as minimal) in the kidney of males at CCI mg/kg/day and increased incidence of hyaline droplet accumulation (graded as minimal) in the kidney tubular epithelium of males at ≥CCI mg/kg/day, both which may be an exacerbation of spontaneous changes. In the urinary bladder epithelium hypertrophy/hyperplasia was noted in of males at ≥CCI mg/kg/ day and females at ≥CCI mg/kg/day. At CCI mg/kg/day there was an increase in mean urine microalbumin and urine clusterin concentration (females only). Changes in urinary biomarkers and microscopic renal findings were considered	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	fully recovered after 8 weeks off-dose, the urinary bladder changes at CCI mg/kg/day were still present after 8 weeks off-dose but occurred with decreased incidence suggesting partial reversal. In a 14 day CCI toxicity study in dogs, minimal to slight degeneration/ regeneration was observed in the kidney with changes in clinical pathology parameters (increased serum urea nitrogen and creatinine) at doses ≥CCI mg/kg/day, these changes also correlated with clinical signs of dehydration as these dose levels were not considered tolerated. In a 39-week toxicity study in dogs there was an increased incidence of non-adverse tubular degeneration/regeneration in males at ≥CCI mg/kg/day and in females at CCI mg/kg/day. These changes were not seen after the 8-week recovery period. Additionally, unclassified urinary crystals were noted in the urine microscopic evaluation of a few animals at CCI mg/kg/day, during the dosing period. **Clinical** During the FTIH (212148) study in healthy participants, there were no reports of any renal associated adverse events. In this	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	study participants received up to CCI mg CCI dose for 7 days.	
Other		
Nitrofurantoin (Macrobid)	The most frequent AEs possibly or probably related to oral nitrofurantoin treatment are nausea (8%), headache (6%), and flatulence (1.5%). There is also a need to monitor for *C. difficile*-associated diarrhea during nitrofurantoin treatment. Refer to locally approved nitrofurantoin prescribing information for specific details relating to nitrofurantoin. Nitrofurantoin is contraindicated for patients with anuria, oliguria, or significant impairment of renal function; pregnant patients at term (38 to 42 weeks' gestation), during labour and delivery, or when the onset of labour is imminent; neonates under 1 month of age; and patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin. Rare adverse reactions that generally occur in patients receiving treatment for 6 months or longer are acute, subacute, or chronic pulmonary reactions, with potential insidious	Monitoring of clinical parameters and AEs (SoA Section 1.3) will be conducted, and treatment monitoring and evaluation criteria (Section 7.1.1) will be utilized to mitigate hepatic effects. The exclusion criteria for this study include contraindications to nitrofurantoin use, exclude participants at risk for nitrofurantoin adverse reactions, and Section 5.2 participants with a history of sensitivity to nitrofurantoin, or components thereof (Section 5.2). Participants must agree not to use antacid preparations containing magnesium trisilicate or uricosuric drugs during study intervention (Section 5.2). Suspected C. difficile infection will be managed according to a prespecified algorithm provided in Section 10.9. Information on the prevalence and duration of effect and onset of actions associated with discolouration is limited. To further minimize the risk of unblinding due to urine discolouration sites will be asked to ensure personnel that are collecting urine samples are separate from personnel conducting the assessment of clinical resolution of symptoms and the personnel conducting the clinical symptom scoring assessments. Precautions related to nitrofurantoin are summarized in detail in the Study Reference Manual.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	development of chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both). Peripheral neuropathy has occurred, which may be enhanced for patients with anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease. Nitrofurantoin has induced the occurrence of hemolytic anemia of the primaquine-sensitivity type, which appear to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Concomitant administration of nitrofurantoin with antacids containing magnesium trisilicate reduces both the rate and extent of absorption, and uricosuric drugs, such as probenecid and sulfinpyrazone, can inhibit renal tubular secretion of nitrofurantoin. Uncommon, side effects include dark coloured urine, changes in facial skin colour. There is little information on the details (e.g.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	prevalence and onset and duration) however, there may be a risk for unblinding within the study.	
Potential increased risk of participants and site staff contracting coronavirus disease 2019 (COVID-19).	Participation within a healthcare environment may increase risk of contracting COVID-19. Exposure to other participants and staff may increase risk of exposure.	While no longer in a pandemic state, depending on incidence rates in the community, COVID-19 (severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]) may pose a challenge to integrity of the trial, protection of participants' rights, safety and wellbeing and the safety of clinical trial staff. Therefore, risk mitigation strategies have been introduced and will be evaluated on an ongoing basis per each country. • Monitoring for the clinical presentation of COVID-19 signs/symptoms. • Conduct study at sites which have appropriate mitigation strategies in place. • Rapid turnaround COVID testing at screening. Parallel PCR testing for 5-day inpatient period in Cohort 1. Rapid Turnaround testing at all other visits requiring COVID testing. See SoA Section 1.3.

2.3.2. Benefit Assessment

2.3.3. Overall Benefit: Risk Conclusion

Potential medical benefit may be derived for participants randomised to the nitrofurantoin arm as this is a recommended treatment for uUTI. Participants randomised to the GSK3882347 arm in this study may not receive any therapeutic benefit as the efficacy profile is unknown. This is a blinded study and Investigator and Participant will not know the randomised treatment assignment. All the participants will be contributing to the development of a potential novel therapy in an area of unmet need.

The anticipated benefits of GSK3882347 are its use will not contribute to the rising resistance rates observed with conventional antibiotic therapies, and, due to its narrow spectrum of activity and mode-of-action, minimal dysbiosis is anticipated.

3. OBJECTIVES AND ENDPOINTS AND/OR ESTIMANDS

Objectives	Endpoints
Primary	
• To assess the microbiological efficacy of GSK3882347 at the Test of Cure (ToC) visit in participants with uUTI who have qualifying *E. coli* at baseline	• Microbiological response at the ToC Visit
Secondary	
• To evaluate the safety and tolerability following CCI [redacted] oral dosing for 5 days of GSK3882347 in participants with uUTI	• Occurrence of adverse events (AEs) and serious adverse events (SAEs) • Clinically significant changes from baseline in laboratory values (hematology, chemistry and urinalysis), vital signs and 12lead electrocardiogram (ECG) readings at each visit
• To evaluate the plasma and urine pharmacokinetic (PK) concentrations following CCI [redacted] oral dosing for 5 days of GSK3882347 in participants with uUTI	<u>Plasma:</u> • GSK3882347 concentration <u>Urine</u> • Urine concentration at 22-24h interval collection post-dose
Exploratory*	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	
• To evaluate the resolution of clinical symptoms over time of GSK3882347 in participants with uUTI caused by *E. coli*	• Clinical resolution response on Day 2 through to Day 6 (when collected and as data permit), ToC and Follow-up Visit
• To evaluate the resolution of clinical symptoms over time of GSK3882347 in participants with uUTI caused by *E. coli* using an exploratory scoring system	• Clinical symptom score outcome and response on Days 1 through to Day 6 (when collected and as data permit), ToC and Follow-up Visit
CCI [redacted]	

Objectives	Endpoints
CCI	

* Details regarding the exploratory analyses will be described in the statistical analysis plan (SAP). Some exploratory data may not be available until after the main database lock and may be analysed/reported separately.

Estimands for Primary Endpoint

The primary clinical question of interest is: *What is the microbiological response for GSK3882347 assessed at ToC in participants with acute uUTI caused by E. coli uropathogens at Baseline who completed the planned course of treatment (5 days) and had no major deviations from protocol that would prevent evaluation of efficacy (as defined in the Study Deviation Rules Document). Use of rescue medication will be set to non-responder in the endpoint definition*

The Primary estimand is described by the following attributes:

- Population: Female participants with acute uUTI with a qualifying baseline *E. coli* uropathogen (Section 10.8) at baseline who completed the planned course of treatment (5 days) and had no major deviations from protocol that would prevent evaluation of efficacy
- Treatment condition: GSK3882347 CCI given orally CCI for 5 days
- Variable: Microbiological response at ToC visit
- Summary measure: Frequency and percentage of participants with microbiological response (responder/non-responder) in GSK3882347 treatment group
- Main intercurrent events anticipated:
  - Use of rescue medication prior to ToC visit- Composite strategy
  - This intercurrent event is captured through the definitions of microbiological response (see Section 9.3.2) and will be considered as non-responders.
  - Participants who are lost to follow-up prior to ToC, have a missing/unevaluable sample at ToC, discontinue study treatment due to any reason (withdrawal of

consent/AEs/missed doses) will not be included in the analysis and may be replaced at the discretion of the Sponsor.

- Rationale for estimand:

Use of rescue medication may impact microbiological outcomes, therefore, the definition of a successful microbiological response precludes the use of rescue medications. In this small, early phase, proof of mechanism study, interest lies in the treatment effect of participants who completed the planned course of treatment and follow important components of the study protocol.

Details of supportive estimands may be provided in the SAP.

Estimand for Secondary Endpoints

The secondary clinical questions of interests are,

1. *To evaluate the safety and tolerability following* CCI *oral dosing for 5 days of GSK3882347 in adult female participants with uUTI*

The estimand is described by the following attributes:

- Population: Female participants with acute uUTI.
- Treatment condition: GSK3882347 CCI given orally CCI for 5 days.
- Variables:
  - Occurrence of adverse events (AEs) and serious adverse events (SAEs)
  - Clinically significant changes from baseline in laboratory values (haematology, chemistry and urinalysis), vital signs and 12 lead electrocardiogram (ECG) readings at each visit.
- Summary measure: Frequency and percentages for AEs, SAEs, laboratory values, vital signs and ECG values.
- Main intercurrent events anticipated:
  - Use of rescue medication -While on treatment strategy
    - Rescue medication could influence safety reporting and therefore, only safety data while participants are taking the study intervention will be considered for the analysis.
  - Discontinuation from the treatment due to any reasons (withdrawal of consent /AEs (if not part of the endpoint definition, for e.g., in AE and SAE)/missed doses)-Treatment policy strategy
    - The occurrence of this intercurrent event is considered irrelevant in evaluating safety, as interest lies in the full safety profile.

2. *To evaluate the plasma and urine PK parameters following* CCI *oral dosing for 5 days of GSK3882347*

The estimand is described by the following attributes:

- Population: Female participants with acute uUTI
- Treatment condition: GSK3882347 given orally CCI [redacted] for 5 days
- Variables:
  - Plasma:
    - CCI [redacted]: AUC(0-inf), Cmax, and tmax collected on Day 1
    - CCI [redacted] Day 5 AUC (0-24), Cmax, and tmax collected following 5th dose, pre-dose Ctau and AUC(0-tau)
    - Urine:
    - Urine concentration at 22-24h collection following dose on Day 1 and Day 5, as data permit
    - Amount excreted in urine (Ae) of unchanged GSK3882347, fraction of the dose excreted in urine (fe), and renal clearance (CLr), as data permit.
- Summary measure: Mean, 95% confidence interval (CI), standard deviation (SD), median, minimum and maximum for non-transformed data of all PK parameters. Geometric mean, 95% CI of geometric mean, SD and coefficient of variation (CV) of geometric mean, for log transformed data for all PK parameters except for Tmax.
- Main intercurrent events anticipated:
  - Use of rescue medication
  - Discontinuation from the treatment due to any reasons (AEs/withdrawal of consent/missed doses)

All these intercurrent events will be handled using while on treatment strategy as PK data will be collected only when participants are on treatment.

4. STUDY DESIGN

4.1. Overall Design

- This Phase 1b study is a double-blind, double-dummy, nitrofurantoin-controlled study, designed primarily to evaluate microbiological response at the ToC visit and safety, tolerability and PK response following CCI [redacted] oral dosing for 5 days of GSK3882347 in adult female participants with uUTI. Nitrofurantoin will be included in the study to ensure unbiased reporting of safety events. Clinical resolution and clinical symptom score will be part of the exploratory objectives of this proof of mechanism study. A detailed review of the microbiological characterization and time to response will also be explored. Aside from microbiological characterization no formal statistical comparisons of GSK3882347 and nitrofurantoin are planned. CCI [redacted] All participants who provide informed consent and meet the study entry criteria will be randomized to receive either CCI [redacted] GSK3882347 or 100 mg BID nitrofurantoin in a 3:1 ratio. Safety assessments will be conducted throughout the study duration; pre-treatment and post-treatment urine and

plasma PK collections will be performed and appropriate microbiological, clinical CCI [redacted] assessments will also be conducted.

- As this is a first in patient study in women with uUTI, who are essentially otherwise healthy, it was considered a high patient burden to ask all participants to remain in-house for the duration of dosing. Further considerations in the study design included a lack of sites where the study could be run plus the recruitment challenges that mandating an in-house stay would bring. As it is not considered necessary to obtain full PK profiles from every study participant, and to ease participant burden, there will be 2 participant cohorts in the study:
  - Cohort 1 is an inpatient cohort: For this cohort, intensive PK sampling will be conducted during the intervention period and more frequent analyses of microbiological and clinical response to therapy will be assessed.
  - Cohort 2 is an outpatient cohort: The PK, microbiological, and clinical responses to therapy will be assessed less frequently in this cohort.
- It is anticipated that there will be a limited number of Study Sites permitted to recruit Cohort 1, these Sites may also be allowed to enroll Cohort 2 at the same time, as agreed by GSK.
- Participants will consent using the materials corresponding to the cohort they are joining, either Cohort 1 or Cohort 2.
- If at any time during the study, participants experience new or worsening signs and symptoms of UTI, they will be assessed (at site visits or in discussion over telephone, see SoA) and treated per the investigator's judgment.
- The screening period can be up to 24 hours prior to the first day of dosing. The Treatment period will consist of 5 days.
  - Cohort 1 participants will be discharged from the clinic on Day 6 and asked to return for the ToC visit 5-8 days following the last day of dosing. Participants will be asked to attend a Follow-up Visit ~28 days after the start of Treatment. The duration of the study will be approximately 28 days.
  - Cohort 2 participants will attend outpatient visits on Days 1, 2, and 6 and asked to return for the ToC visit 5-8 days following the last day of dosing. Participants will be asked to attend a Follow-up Visit ~28 days after the start of Treatment.

For treatment discontinuation and participant withdrawal, see discontinuation criteria section.

CCI [redacted]
CCI [redacted]

4.2. Scientific Rationale for Study Design

This Phase 1b study is designed primarily to evaluate microbiological response of GSK3882347 in female participants with uUTI. The sample size is not sufficiently large to enable firm conclusions to be made around therapeutic efficacy (clinical and microbiological outcomes and response) in relation to Standard of Care (SoC). However,

it will provide a preliminary assessment of the microbiologic efficacy of GSK3882347 in this patient population. This is important to establish prior to initiating larger Phase 2/3 studies.

As this will be the first study to evaluate GSK3882347 in females with UTI, safety is a key secondary endpoint for the study. The safety of GSK3882347 has previously been evaluated in one FTIH study (212148) and no safety issues were observed; there are no additional safety concerns with this proposed study in participants with ongoing uUTI infection. CCI CCI (see Section 4.3), CCI CCI

Due to the specificity of GSK3882347 for *E. coli,* it is anticipated that its use will not lead to the dysbiosis caused by other treatments which also eradicate other genera such as Lactobacillus, which are important in maintaining gut homeostasis and are protective against UTI. This in turn should lead to reductions in the overgrowth of bacteria and yeast in the vagina, e.g. *Candida albicans* which is a common consequence of antibiotic therapy and can itself lead to long term issues with recurrence. CCI

4.3. Justification for Dose

GSK3882347

The oral GSK3882347 dose in this study is CCI CCI for 5 days. A 5-day dosing duration is in alignment with current treatment guidelines for efficacious antibacterial treatment of uUTI in women, which typically ranges from 3 to 7 days [Gupta, 2011, NICE, 2018, EAU, 2024]. The safety and tolerability of oral doses up to CCI CCI CCI has been evaluated in Phase 1 Study 212148 and there were neither SAE reports nor clinically significant changes in the laboratory data, vital signs, or electrocardiogram. All reported AEs were mild/moderate in intensity and had fully resolved by the time of participant discharge from the study.

CCI . CCI CCI CCI CCI

CCI
CCI
CCI
CCI However, unlike traditional antibiotics, GSK3882347 is a novel, bacterial attachment inhibitor for which translation from the murine acute cystitis model has not been validated in patients with acute uTI. CCI
CCI
CCI
CCI Given that the bladder is the site of action of GSK3882347, the use of GSK3882347 urine PK data is appropriate for selecting the GSK3882347 CCI CCI oral dose for 5 days for study in the treatment of participants with uTI.

CCI
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CCI

Mean plasma exposure following a dose of CCI × CCI was below the safety margin established in the rat 14-day GLP toxicity study, No-observed-adverse-effect Level (NOAEL) of CCI /kg/day. There was 4-fold and 3-fold coverage for Day 1 and Day 7 AUC(0-24), respectively; there was 3.4-fold and 3.1-fold coverage to the Day 1 and Day 7 Cmax, respectively.

CCI

Nitrofurantoin (Macrobid)

The oral nitrofurantoin dose in this study is 100 mg BID, a total daily dose of 200 mg, for 5 days. The label indicates, for treatment of uTI caused by susceptible strains of *E. coli* or *S. saprophyticus,* in adults and paediatric patients over 12 years of age, a 100 mg BID dose for up to 7 days (refer to locally approved prescribing information). The labelled 7-day dosing duration of nitrofurantoin was based on clinical registration studies from several decades ago. More recently, a 5-day dosing duration of nitrofurantoin was shown to be efficacious for the treatment of uTI in women [Gupta, 2007] and a treatment duration of 3-5 days for nitrofurantoin is in alignment with current treatment guidelines [Gupta, 2011, NICE, 2018, EAU, 2024].

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study it is expected to be the last scheduled procedure shown in the Schedule of Activities for the last participant in the study at the Follow-up Visit.

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age

a. Participant must be ≥18 years of age and ≤70 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

b. The participant has 2 or more of the following clinical signs and symptoms of uUTI with onset <96 hours of the screening assessment: dysuria, frequency, urgency, or lower abdominal pain.

c. The participant has nitrite OR pyuria (≥10 WBC/mm^3 OR >5 WBC/HPF OR the presence of at least 2+ leukocyte esterase) from a pre-treatment clean-catch midstream urine sample based on local laboratory procedures.

Weight

d. Body mass index (BMI) ≥19.0 kg/m^2).

Sex and Contraceptive/Barrier Requirements

e. A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

   - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4: Contraceptive and Barrier Guidance.

   OR

   - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period and for at least 3 days after the

last dose of study intervention or 5 days after the last dose of study intervention for WOCBP choosing hormonal contraceptives (including double barrier contraception as stated in Section 10.4). The investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine as required by local regulations) before the first dose of study intervention. See Section 8.2.5 Pregnancy Testing
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

f. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Positive highly sensitive urine pregnancy test at screening.
2. Women that are currently lactating and or breast feeding.
3. The participant has a BMI ≥40.0 kg/m^2 or a BMI ≥35.0 kg/m^2 with obesity-related health conditions such as high blood pressure or uncontrolled diabetes (defined as a non-fasting glucose value >300 mg/dL or based on investigator judgment).
4. The participant is immunocompromised or has altered immune defenses that may predispose the participant to a higher risk of treatment failure and/or complications (e.g., renal transplant recipients, participants with clinically significant persistent granulocytopenia [absolute neutrophil count <1000/µL], and participants receiving immunosuppressive therapy, including corticosteroid therapy [e.g. ≥40 mg/day prednisolone or equivalent for >1 week or; prednisolone or equivalent ≥20 mg/day for >2 weeks or; prednisolone or equivalent ≥10 mg/day for >6 weeks]).
5. The participant has 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). Participants who have had a gastric bypass or a cholecystectomy are excluded from the study.
6. 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 any

Enterobacterales other than *E. coli* [redacted] as the contributing pathogen.

7. The participant has symptoms known or suspected to be caused by another disease process, such as asymptomatic bacteriuria, overactive bladder, chronic incontinence, or chronic interstitial cystitis, that may interfere with the clinical efficacy assessments.
8. 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 vesicoureteral reflux, detrusor insufficiency).
9. The participant has an indwelling catheter, nephrostomy, ureteral stent, or other foreign material in the urinary tract.
10. The participant who, in the opinion of the investigator, has an otherwise complicated UTI, an active upper UTI (e.g., pyelonephritis, urosepsis), signs and symptoms onset ≥96 hours before the screening assessment, or a temperature ≥101°F/38°C, flank pain, chills, or any other manifestations suggestive of upper UTI.
11. The participant has anuria, oliguria, or significant impairment of renal function (eGFR-<60 mL/min/1.73m^2 [calculated using CKD-EPI 2021; Inker, 2021] or serum creatinine >1.5 x upper limit of normal [ULN] at screening). Note*: Please reference the Study Reference Manual for guidance on calculating the eGFR during screening.*
12. The participant presents at enrollment with a suspected sexually transmitted infection.
13. The participant has congenital long QT syndrome or known prolongation of the corrected QT (QTc) interval.
14. The participant has uncompensated heart failure, defined as New York Heart Association Class ≥III.
15. The participant has severe left ventricular hypertrophy.
16. The participant has a family history of QT prolongation or sudden death.
17. The participant has a recent history of vasovagal syncope or episodes of symptomatic bradycardia or bradyarrhythmia within the last 12 months.
18. The participant has a QTc >450 msec or a QTc >480 msec for participants with bundle-branch block. **Note**: The QTc is the QT interval corrected for heart rate according to Fridericia formula, machine, or manual overread.
19. The participant has an alanine transferase (ALT) value >2 × ULN.
20. The participant has a bilirubin value >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
21. 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 viral hepatitis or moderate-to-severe liver insufficiency (Child Pugh class B or C).

22. History of positive human immunodeficiency virus (HIV) antibody or antibody/antigen test.
23. History of presence of Hepatitis B surface antigen (HBsAg) within 3 months prior to first dose of study intervention.
24. History of Hepatitis C antibody test result within 3 months prior to first dose of study intervention.

- **NOTE**: Participants with a history of a positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if there is a history of a confirmatory negative Hepatitis C ribonucleic acid (RNA).

25. History of a Positive Hepatitis C RNA test result within 3 months prior to first dose of study intervention.
26. Substance abuse: Active substance abuse or a history of substance abuse (in the opinion of the Principal Investigator) within 6 months prior to the initial Screening visit. Note that *documented* medical use of marijuana or occasional recreational use of marijuana is permitted.
27. A positive confirmation of COVID-19 infection, or high clinical index of suspicion for COVID-19.
28. The participant has a history of significant cardiac, endocrinologic, haematologic, pulmonary, metabolic, renal (including significant or chronic proteinuria, but excluding transient proteinuria in the setting of infection), hepatic, immunologic, urologic, neurologic, dermatologic, psychiatric or gastrointestinal conditions that, in the opinion of the investigator places the participant at unacceptable risk or would make adhering to study procedures for the duration of the study difficult.

Prior/Concomitant Therapy

29. The participant has received treatment with other systemic antimicrobials or systemic antifungals within 1 week (or 10 weeks for dalbavancin or oritavancin before study entry).
30. The participant does not agree to adhere to the concomitant therapy restrictions as described in Section 6.8.2 from the Screening Visit through to the Follow-Up Visit.

Prior/Concurrent Clinical Study Experience

31. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days.
32. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
33. Current enrollment or past participation within the last 30 days or 5 half-lives, whichever is longer, before signing of consent in any other clinical study involving an investigational study intervention or any other type of medical research.

Other Exclusions

34. The participant resides in a nursing home or dependent care-type facility.
35. The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete study follow-up.
36. Regular alcohol consumption within 6 months prior to the study defined as:
    - An average weekly intake of >14 units for females.
    - One unit is equivalent to approximately to 8 g of alcohol: a half-pint (250 ml) of beer, one glass (125 mL) of wine or one (35 mL) measure of spirits.

38. Known hypersensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.
39. Contraindication for nitrofurantoin. E.g., hypersensitivity to the active substance, other nitrofurans or to any of the excipients, renal dysfunction, known Glucose-6-phosphate Dehydrogenase (G6PD) deficiency, acute porphyria.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Dietary restrictions:

- There are no known or predicted dietary restrictions for GSK3882347 however, because nitrofurantoin will be a blinded comparator in the study and it is recommended to take with food (e.g. at mealtimes), the same advice will be given to all study participants.
- Water is allowed as desired except one hour before and two hours after dosing, except for the glass of water needed to administer the study intervention (e.g. maximum 240 mL).
- Participants should not alter their usual dietary habits (including alcohol consumption and tobacco use) from their considered normal whilst participating in the study including during the on-treatment phase (from start of screening until the Day 5 22-24 h PK samples have been taken on Day 6).
- Participants should not take dietary or herbal supplements, probiotics (drinks/tablets), antacid preparations containing magnesium trisilicate, uricosuric drugs or alternative medications for the treatment of uUTI (including cranberry juice or tablets/capsules, methenamine hippurate, D-mannose) until completion of the Follow-up Visit, unless, in the opinion of the investigator and Medical Monitor, the medication will not interfere with the study.

5.3.2. Other Lifestyle Restrictions and Recommendations

- Participants will be requested to abstain from sexual activity from the Screening Visit through the ToC Visit to prevent possible re-infection.
- Participants should not alter their usual hygiene habits from their considered normal (e.g. new washing routine or sanitary products) from the Screening Visit through the ToC Visit.
- Participants will be requested to adhere to local COVID-19 prevention advice for the purpose of minimizing any potential risk of infection and potential outbreak at study sites and exposure to other participants and staff. Participants will be monitored for clinical presentation of COVID-19 signs and symptoms and will be asked to communicate any signs or symptoms to the site prior to site visits.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the reason for screen failure is:

- An ECG or lab value that, in the opinion of the investigator and/or Medical Monitor, is spurious or needs to be reconfirmed.
- Scheduling of Day 1 visit falls outside of 24 hrs; however participant will remain within 96 hours of symptom onset.

This reconfirmation should only be conducted once and if the participant does not meet the inclusion criteria following this second analysis, they will be deemed a screen failure. If the participant meets the study inclusion criteria following this repeat analysis they will retain the original participant number.

Individuals with an acute UTI who do not meet all of the criteria for participation in this study (screen failure), who are not randomised and do not receive GSK3882347, may be considered for future study enrollment if they have a subsequent UTI infection provided the original UTI infection had been appropriately treated with SoC and the subsequent infection was at least 4 weeks after the resolution of the original UTI infection. If such a situation arises, inclusion of the participant in the study should be discussed on a case-by-case basis with the medical monitor. In this situation, a participant should only be rescreened once.

Rescreened participants should be assigned a new participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

There are no planned criteria for temporarily delaying the study. Section 6.5. Dose Modification contains instructions for unplanned events.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

Table 1 Study Intervention(s) Administered

Intervention Label		
Intervention on Label	**GSK3882347+ Placebo**	**Nitrofurantoin + Placebo**
Intervention Description	Active Pharmaceutical Ingredient (API) alone and with placebo to match Nitrofurantoin dosing schedule (100 mg BID).	Nitrofurantoin alone and with placebo to match GSK3882347 dosing schedule.
Type	Drug	Drug
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	CCI	100 mg/capsule
Dosage Level(s)	CCI [redacted]	100 mg BID CCI [redacted]
Total Duration	Participants will receive CCI CCI for 5 days	Participants will receive 100 mg BID for 5 days
Route of Administration	Oral Study medication will be administered by the study personnel (or self-administered in Cohort 2) during each dosing day with approximately 240 mL of water and with food.	Oral Study medication will be administered by the study personnel (or self-administered in Cohort 2) during each dosing day with approximately 240 mL of water and with food.
Use	Experimental, Placebo	Safety-comparator, Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the GSK	Provided centrally by the GSK
Packaging and Labeling	Study intervention will be provided in High Density Polyethylene (HDPE) bottles. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in HDPE bottles. Each bottle will be labeled as required per country requirement.

*Please refer to the SRM for further guidance on the Dose A and Dose B drug administration interval.

6.2. Preparation, Handling, Storage and Accountability

Details on storage, handling, and allowable excursions for GSK3882347 investigational product (IP), nitrofurantoin and Placebo will be provided in the Technical Terms of Supply (TTS). Storage for IP and nitrofurantoin is room temperature (not to exceed 30ºC).

1. A description of the detailed methods and materials required for preparation of GSK3882347, nitrofurantoin and Placebo are provided in the TTS.
2. The capsules will be provided by GSK as per instructions in the TTS that will be reviewed and approved by GSK prior to use.
3. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
4. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
5. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
6. Further guidance and information for the final disposition of unused study intervention are provided in the Technical Agreement.
7. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
8. A Safety Data Sheet /equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a randomized double-blind study and participants will be randomized to receive either GSK3882347 CCI [redacted] for 5 days or nitrofurantoin in a 3:1 allocation ratio using an interactive response technology (IRT). All participants will be randomized before the study is initiated, information and directions for the IRT will be provided to each study site. As the study treatment taken during the study will be double-blinded, neither the participant nor immediate study personnel (i.e., investigators,) will know which study treatment the participant is receiving. CCI [redacted]
CCI [redacted]
CCI [redacted]

On the day the patient is to receive the first dose of study intervention, a designated member of the site staff will contact the IRT to obtain the study treatment assignment and dispense therapy accordingly. A patient is considered randomized when the site personnel receive the treatment assignment associated with the patient entered into the IRT.

A participant may continue in the study if that participant's intervention assignment is unblinded. The event or condition which led to the unblinding will be recorded in the case report form (CRF).

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

6.4. Study Intervention Compliance

COHORT 1

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

COHORT 2

- When participants self-administer study intervention(s) at home, compliance with randomized study intervention will be assessed by direct questioning and collection of diary cards (Section 8.2.6) during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.
- A record of the quantity of randomised study intervention dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded.

6.5. Dose Modification

No dose modifications will be permitted.

The Principal Investigator and the GSK Medical Monitor will review the following and dosing will be temporarily halted, and no further participants will be dosed until a full safety review of the data has taken place if:

- One (1) or more participants experience a SAE which has a reasonable possibility of being causally related to study intervention.
- Two (2) or more participants experience a severe or clinically significant non-serious adverse event (based upon investigator judgment) which has a reasonable possibility of relation to study intervention.
- Three (3) or more participants experience the same adverse event of moderate severity which has a reasonable possibility of relation to study intervention.

Relevant reporting and discussion with the medical monitor, relevant personnel, and if it is considered necessary an independent safety review committee comprising GSK senior physicians not directly involved in the study, will take place before resumption of dosing.

The above criteria will apply even if measured PK parameters are below the pre-specified PK stopping criteria, and every effort will be made to take a blood sample at the time of the AE for PK analysis.

6.6. Continued Access to Study Intervention after the End of the Study

Following the study there will be no further intervention.

6.7. Treatment of Overdose

GSK does not recommend specific treatment for an overdose with GSK3882347. There is no specific antidote for overdose with a FimH inhibitor. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

Occasional incidents of acute overdosage of nitrofurantoin have not resulted in any specific symptoms other than vomiting (refer to locally approved prescribing information). Induction of emesis is recommended. There is no specific antidote, but a high fluid intake should be maintained to promote urinary excretion of the drug. Refer to the drug label for overdose information regarding nitrofurantoin.

In the event of an overdose, the investigator/treating physician should withhold from further dosing and:

1. Contact the GSK medical monitor immediately.
2 Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3882347 can no longer be detected systemically (at least 3 days).
3 Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4 Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

6.8. Concomitant Therapy

6.8.1. Permitted Medication and Non-Drug Therapies

Permissible medicines are Paracetamol or Acetaminophen, at doses of ≤2 grams/day, which may be used at any time during the study and topical (including suppository) anti-fungal creams (e.g. miconazole, nystatin) may be used to treat symptoms in those participants who develop vulvovaginal candidiasis.

Female contraception is permitted in accordance with the guidance provided in Section 10.4.

Concomitant medications not specifically prohibited in the study (See Section 6.8.2 below) are permitted in line with the exclusion criteria. The medical monitor should be contacted if there are any questions about the permitted and prohibited medications.

6.8.2. Prohibited Medication and Non-Drug Therapies

Treatment with systemic antimicrobials or systemic antifungals within 1 week (or 10 weeks if dalbavancin or oritavancin) prior to study entry is prohibited and participants should not start any new probiotic capsules/tablets during the study to prevent any potential alterations in the gastrointestinal or vaginal microbiome.

Participants may not receive the following treatments within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the first dose of the study until completion of the follow-up visit:

- Antacid preparations containing magnesium trisilicate, uricosuric drugs, vitamins and dietary or herbal supplements
- Alternative medications for the treatment of uUTI (including cranberry juice or tablets/capsules, methenamine hippurate, D-mannose)
- Any medications which are strong inhibitors of cytochrome P450 enzymes (including oral treatments for vulvovaginal candidiasis, e.g. fluconazole)
- Any medications which inhibit OAT3 (e.g. diflunisal, probenecid)
- Potassium containing compounds for the treatment of bladder symptoms.
- Immunosuppressants (as described in the exclusion criteria #4, Section 5.2)
- Drugs which have the potential for DDIs with nitrofurantoin, e.g. quinolone antibiotics.
- Known nephrotoxic medications are prohibited (e.g. ACE inhibitors, Angiotensin receptor blockers) and regular NSAID use should be avoided.

In vitro, GSK3882347 mediated the induction of CYP3A4, CYP2B6 and 2C9 in human hepatocytes. The risk of GSK3882347 perpetrating a clinical drug-drug interaction (DDI) when co-dosed with substrates sensitive to induction of CYP3A4, CYP2B6 & CYP2C9 was evaluated using mechanistic static equations per the regulatory guidance (FDA & EMA); the data suggested that GSK3882347 had the potential to be a moderate inducer of CYP3A4 in the clinic (% decrease in AUC of sensitive substrate ≥50 - <80) and a weak inducer of CYP2B6 and CYP2C9 (% decrease in AUC of sensitive substrates <50). Thereafter, although a thoroughly verified and qualified GSK3882347 PBPK model predicted that there was no risk of CYP induction-mediated DDIs with sensitive CYP substrates, including ethinyl estradiol, it is proposed to mitigate the risk of CYP3A4 induction with a formal clinical DDI study at a later date. Notwithstanding, sensitive substrates (with the exception of oral contraceptives) of CYP3A4, 2B6 and 2C9 should be excluded (see FDA table of sensitive substrates (Table 2.1)).

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1

6.8.3. Rescue Medicine

If participants do not respond clinically (participants experience new, worsening or non-resolving signs and symptoms of uUTI) to randomised medication, they should be given rescue medication. They will be considered a treatment failure and will be provided rescue medication by site as per SoC [Gupta, 2011].

Use of rescue medications is allowable at any time during the study. The requirement for the use of rescue medications should be assessed by the Investigator in accordance with site procedure and treatment guidelines [Gupta, 2011]. If clinically acceptable (and onset of a severe infection is not suspected), rescue medication should be postponed until the next clinical symptom resolution assessment during the On-Therapy period.

Pathogen identification or in vitro resistance of recovered uropathogens alone, is not a reason for study treatment discontinuation through the On-Therapy period. Patients can resolve their infection spontaneously and in the absence of treatment [Little, 2009].

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Rescue medication to be prescribed by Site Investigator as required and as assessed by the Investigator and in consultation with the Medical Monitor if required by the Investigator. The decision to prescribe rescue medication resides with the Investigator. A combined clinical and laboratory (e.g. serum creatinine and other haematological and biochemical parameters) assessment should be used to prior to withdrawal of study intervention.

The Investigator can request the participant's baseline, enrolling microbiology culture to help in the assessment and additional suitable SoC if required [Gupta, 2011]. Note: The potential for a drug-drug interaction with next line therapy (e.g., trimethoprim-sulfamethoxazole) has been reviewed and is permitted in the study.

If antibiotic rescue medication is given, the participant will complete an early discontinuation visit as per the SoA and will not be required to attend any other subsequent visits.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.9.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. All Participants who discontinue study intervention should have an early withdrawal/discontinuation visit. Plasma and urine PK sample(s) should be collected as per SoA on the corresponding day as the participants last day of PK sample collection (s).

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 (Section 6.8.3. Rescue Medication).

Reasons for study intervention discontinuation may include the following:

- Adverse event
- Investigator discretion
- Lost to follow-up
- Participant decision
- Participant reached protocol-defined stopping criteria.

The reason for study intervention discontinuation will be recorded in the eCRF.

Participants who discontinue study intervention for the reasons above, but not due to the requirement of rescue medication, will not be considered withdrawn from the study and should attend all subsequent study visits (see Section 1.3). They will remain in the study to be evaluated for safety and efficacy, PK samples will not be collected following the treatment discontinuation and early withdrawal/discontinuation visit. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If study intervention is permanently discontinued due to the requirement of rescue medication, the participant will complete an early study discontinuation visit and no other visits will be required.

7.1.1. Liver Chemistry Stopping Criteria

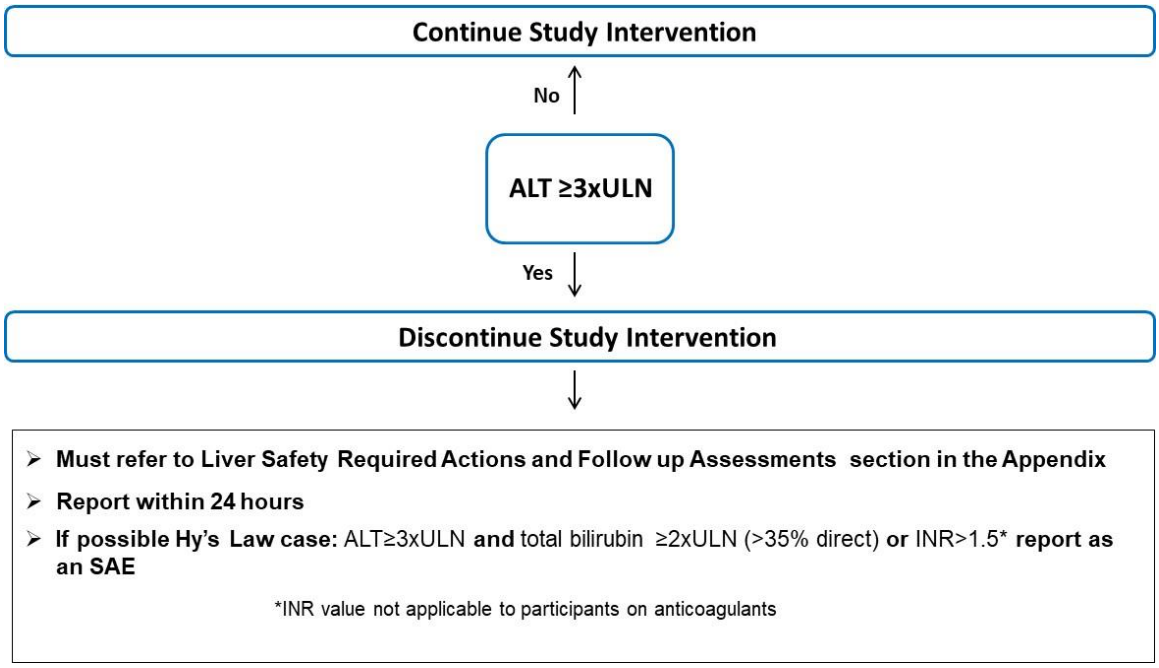
Liver chemistry stopping criteria with increased monitoring and follow-up assessments have been designed to assure participant safety and evaluate liver event etiology.

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

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

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met

Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

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

7.1.2. QTc Stopping Criteria

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

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

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

Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
<450 msec	>500 msec
450 – 480 msec	≥530 msec

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

7.1.3. Study Specific Stopping Criteria

Participants who report symptoms suggestive of COVID-19 while in the study and research unit should adhere to local COVID-19 isolation and or prevention advice and where applicable tested for SARS-CoV-2 infection using an approved test. Sites local COVID-19 related procedures should be followed.

Withdrawal of participants from the study will be at the discretion of the Principal Investigator or designee, but should first be discussed and agreed with the GSK Medical Monitor. Further study related procedures, except those required for participant safety and well-being, should be paused until the discussion is complete.
Participants who test positive for SARS-CoV-2 infection during the course of the study will be withdrawn (after discussion with the GSK Medical Monitor and Principal Investigator [PI]) and will be replaced at the discretion of the Sponsor and in consultation with the PI.

7.2. Participant Discontinuation/Withdrawal from the Clinical Study

- A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.
- At the time of discontinuing from the study, if possible, an early discontinuation/ withdrawal visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.

- All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be available for 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 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, they can 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 from the study will be documented in the eCRF based on the list below:
    - Adverse event
    - Investigator discretion
    - Lost to follow-up
    - Participant decision
    - Participant reached protocol-defined stopping criteria
- Participants who are discontinued from the study because of AEs/SAEs must be clearly distinguished from participants who are discontinued for other reasons. Investigator will follow participants who are discontinued from the study due to an AE/SAE until the event is resolved.

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's registered 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, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants who have signed informed consent but are not eligible to proceed should 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 ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA. A pre-screen is available if required for the collection of a urine sample to determine eligibility based on a urinalysis dipstick for pyuria and nitrite and pregnancy.

To minimize the amount of time that participants spend at the clinic, e-Consent may be utilized. The site may use an electronic method to obtain participant signatures as long as it conforms to 21 CFR Part 11 and is approved by IRB.

Laboratory and analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel unless rescue medication is necessary or until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

1. 12-lead ECG
2. Vital signs & physical exam
3. Clinical symptom resolution and clinical symptom scores

4. Urine microbiology collections
5. Pharmacokinetic urine collections
6. Pharmacokinetic and safety sample and blood draws (haematology, chemistry and urinalysis, to be conducted after clinical symptom scores at screening)
7. CCI [redacted]

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

8.1.1. Clinical Evaluation: Symptom of uUTI and Clinical Resolution Response

Clinical Symptoms

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				
Frequency				
Urgency				
Lower abdominal or suprapubic pain				

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

At screening the participant must present with at least 2 signs and symptoms and have a total cumulative symptom score ≥2 for randomisation to the study. There are 4 symptoms categories, including: Dysuria, Frequency, Urgency and Lower abdominal or suprapubic pain. Each Category is scored from 0 -3. There is a cumulative maximum score of 12.

The baseline assessment is collected at the Day 1 pre-dose visit. If the baseline assessment is on the same day as the screening assessment, the assessment will be considered the screening and baseline score. In this case, the scoring assessment must also meet the inclusion criteria. This clinical symptom score will be assessed again at each visit post first dose and at the ToC and Follow-up Visit (see SoA).

The clinical signs and symptom score outcome at each visit will be the cumulative score from the clinical symptom table. Clinical symptoms success is defined as normal presentation of symptoms with a total cumulative signs and symptom score of zero. The time to clinical response will be investigated and key timings for assessment is the ToC and Follow-up Visit.

Clinical Resolution Response

For the assessment of clinical resolution, the Investigator will be asked to record their impression of the clinical status of the participant (resolved/unresolved). The rationale being, that resolution using the clinical symptom score may not necessarily result in a total score of zero (e.g. if a participant has high frequency at baseline, they would never reach a score of 0, yet they may have achieved clinical resolution as assessed by the Investigator). The clinical resolution response is the definitive outcome over clinical symptom scores.

When possible, the same Investigator will determine the clinical resolution for each participant at each visit post first dose of Treatment. Clinical resolution response (resolved/unresolved) will be determined at the ToC and Follow-up Visit.

Clinical resolution is defined by the following: in the opinion of the Investigator there is resolution of signs and symptoms of the uUTI present at Baseline (and no worsening and no new signs and symptoms) and no requirement for the use of other antimicrobial therapy.

For participants who are considered unresolved by the Investigator, additional questions may be asked regarding their uUTI signs and symptoms.

8.1.2. Microbiology Outcome and Response

- **Urine and Microbiology: Bacteriology Samples**

Urine for inclusion criteria, associated with microbiology

For inclusion into the study, a urine analysis sample is collected during safety assessments, which will be used to confirm nitrite or pyuria (≥10 WBC/mm3 or >5 WBC/HPF or the presence of at least 2+leukocyte esterase) from a screening/ pre-dose clean-catch midstream urine sample per local laboratory procedures. Note: Repeat baseline urine samples are allowed if contamination, defined as ≥10 squamous epithelial cells, is observed under microscopic evaluation.

Urine for microbiology bacteriology

For the microbiology bacteriology samples, a baseline pre-treatment sampling from a clean-catch midstream urine sample will be obtained from all randomized participants. Samples will be sent to a central laboratory for Gram stain, quantitative bacteriological culture, isolate identification, and quantitative PCR (to explore potential FimH-containing Enterobacterales e.g. *E. coli*). Baseline qualifying *E.coli* bacteria (Section 10.8) and the analysis population is defined in the statistics section and will be assessed after randomisation and dosing in the study.

As per the SoA, at the On-therapy (pre-dose collection), ToC, and Follow-up Visits, a clean-catch midstream urine sample will be obtained and sent to a designated central laboratory(ies) for Gram stain, quantitative bacteriological culture, and isolate identification.

CCI [redacted].

- **Microbiological Outcome and Response**

Only those participants who have a qualifying *E. coli* identified at Baseline at a level of $\geq 10^4$ CFU/mL will be evaluated for microbiological outcome and response (Microbiological Modified Per Protocol [Micro-MPP] population).

Microbiological outcomes capture the highest level of granularity per participant and timepoint combination. Each outcome category will be mapped to an associated response category for that participant and timepoint combination (multiple outcomes can be mapped into the same response category). The statistical analyses use the microbiological response variable but the associated microbiological outcome variables are used to analyse the data in more detail via descriptive tables/listings and figures. The algorithms that list and define each microbiological outcome and associated microbiological response may vary by timepoint.

The microbiological outcome is determined by comparing the Baseline culture results to the culture results at each subsequent visit. The absolute CFU counts will be recorded at each applicable visit to enable different algorithms to be evaluated via sensitivity analyses (e.g. to evaluate the treatment effect when using qualifying criteria of $\geq 10^4$ CFU/mL for *E.coli*).

The corresponding microbiological response will also be measured. Microbiological success is defined as a reduction in Baseline culture to $<10^3$ CFU/mL without the participant receiving other systemic antimicrobials. Participant level microbiological response will be determined by statistical programming.

Note: Additional uropathogen combinations / definitions of qualifying pathogens may be explored for microbiological outcome and response (e.g. to evaluate whether GSK3882347 has efficacy when there is also a co-infection with a non *E. coli* uropathogen, or if it has efficacy against any FimH expressing uropathogens).

CCI

[redacted]

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded (height and weight only at screening exam).

8.2.2. Vital Signs

- Vital signs (to be taken before blood collection for laboratory tests) will include tympanic-measured temperature, pulse and respiratory rate, systolic and diastolic blood pressure.
- Blood pressure and pulse measurements will be assessed in a semi-supine or seated position (dependant on site standard practice) with a completely automated device. Manual techniques will be used only if an automated device is not available. (consistency of assessment at each site is requested for each participant throughout the study)
- Blood pressure and pulse measurements should be assessed after at least 10 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

- Blood pressure measurements and pulse, when measured in triplicate as in the SoA, will consist of 3 consecutive readings recorded at intervals of at least 1 minute and the average of the 3 readings will be recorded on the CRF.

8.2.3. Electrocardiograms

- The screening assessment is also considered the baseline assessment.
- Triplicate (screening) and Single (all other study visits unless QTc flag detected) 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.2.4. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 3 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- 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 (see Section 10.3.1 and Section 10.3.2).
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.4.1. Suspected Clostridioides difficile infection

As per nitrofurantoin prescribing information there have been reports of *C.difficile* infections, through the study routine monitoring of clinical parameters and AEs will be conducted to mitigate and assess gastrointestinal effects. If the investigator suspects *C.difficile* infection and or *C.difficile*-associated diarrhea during nitrofurantoin/GSK3883247 treatment, a stool sample will be collected and sent for processing at local labs in accordance with local site testing.

Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in Section 10.9.

8.2.4.2. Management of participants with changes in serum creatinine

Automatic lab alerts will be sent by the central lab to the investigator and Medical Monitor for increased levels of serum creatinine >1.5× compared to baseline levels.

Upon receipt of the automatic lab alert, the investigator should perform:

- clinical assessment (e.g. symptoms improvement or deterioration)
- physical examination
- repeat lab tests (urinalysis, hematology and chemistry including any additional inflammatory markers) as a split sample (send to local and central lab)

Such assessments will be performed as soon as possible and may require participants to return to clinic as an unscheduled visit, if after clinic constrained intervention period for cohort 1 or a non-visit day for cohort 2.

This will also trigger case discussion between the investigator and Medical Monitor (e.g. by phone or email) to ensure assessments are initiated after the flag, to discuss status of the participant and additional appropriate management will be initiated by the investigator (e.g. no actions required, switch to daily monitoring, discontinue study medication, oral rehydration, or others).

8.2.5. Pregnancy Testing

Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.

Pregnancy testing (urine) should be conducted during study intervention period as noted in SoA.

Pregnancy testing (urine) should be conducted at the end of relevant systemic exposure.

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.

8.2.6. Diary Card

A paper diary card will be issued to all participants randomised into Cohort 2 on Day 1. The diary card will be used to collect medication compliance data and conmeds whilst on therapy. The data from the diary card will be used to discuss compliance and conmeds information with the participant and will be entered into the eCRF.

The participant will be asked to bring the diary card with them at each On-Therapy visit. If diary card is forgotten at any visit, compliance and conmeds should be discussed at the visit and recorded in the participant source documents and entered into the eCRF. The participant should be reminded to bring the diary card to the next visit.

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

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention or study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.4

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

- All AEs and SAEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in Section 10.3.4 Updating of SAE and pregnancy information after removal of write access to the participant's eCRF.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB/ package insert and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

Table 2 Timeframes for submitting SAE and pregnancy reports to GSK

Type of event	Initial reports	Follow-up of relevant information on a previous report		
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	Paper/electronic AEs report	24 hours*	Paper/electronic AEs report
Pregnancies	24 hours*	Paper pregnancy notification report/electronic pregnancy report	24 hours*	Paper pregnancy follow-up report/electronic pregnancy report

Type of event	Initial reports	Follow-up of relevant information on a previous report		
	Timeframe	Documents	Timeframe	Documents

AE = Adverse event; CRF/eCRF = Case report form/electronic case report form; **SAE = Serious adverse event.**
*** Timeframe allowed after receipt or awareness of the information by the investigator/site staff.**
‡ 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.**

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until at least 3 days after the last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3. and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

8.3.7. Contact information for reporting SAEs, pregnancies and study holding rules

Table 3 Contact information for reporting SAEs, pregnancies and study holding rules

Study contact for questions regarding SAEs, pregnancies and SAEs linked to device deficiencies. Contact GSK's local and/or medical contacts	Study contact for reporting of study holding/stopping rules If a holding/stopping rule is met, the investigator must immediately inform the GSKs local and/or medical contacts.
Contacts for reporting SAEs, pregnancies and SAEs linked to device deficiencies. Available 24/24 hours and 7/7 days uk.gsk-rd-gcsp-ctsm-admin@gsk.com	Backup study contact for escalation of holding/stopping rules. Refer to the local study contact information for backup contacts.

GSK = GlaxoSmithKline Biologicals SA; SAE = Serious adverse event.

8.3.8. Adverse Events of Special Interest

There are no adverse events of special interest in this study.

8.3.9. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up

8.4. Pharmacokinetics

PK Urine Sample Collection

- Urine samples will be collected as specified in the SoA. The time will be recorded for each urine sample collected, and the total urine volume for each participant will be recorded over the collection time period.
- From each urine PK interval, a 1 mL aliquot of urine will be collected for PK analysis and stored at approximately 70ºC or colder.

PK Plasma Sample Collection

- Whole blood samples of approximately 1 mL will be collected for measurement of plasma concentrations as specified in the SoA.

- Samples will be used to evaluate the PK of GSK3882347. Samples collected for analyses of study intervention plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Residual PK Plasma samples may be analyzed for other compound-related metabolites and the results reported under a separate in vivo/in vitro (IV/IVT), GSK protocols.
- Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.4.1. Pharmacodynamics

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8.5. Genetics

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

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

See Section 10.5. Genetics and Pharmacogenomics for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are not conducted in this study.

8.8. Health Economics

Health economic parameters are not evaluated in this study.

8.9. Administrative and general/baseline procedures

8.9.1. Collection of demographic data

Record demographic data such as year 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.

8.9.2. Medical history

Obtain the participant's medical history by interviewing the participant/LAR(s) and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

9. STATISTICAL CONSIDERATIONS

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

No formal statistical hypotheses will be tested in this study.

9.2. Analysis Sets

For purposes of analysis, the following populations are defined.

Population	**Description**
Randomized Population	All participants randomly assigned to study intervention.
Safety Population	All randomized participants who receive at least 1 dose of study intervention. Participants will be analyzed according to their actual intervention received.
PK Population (Sub populations identified for Cohort 1 and Cohort 2)	All randomized participants who have a valid PK sample taken and from whom a measurable plasma or urine concentration, even if the concentration below assay's limit of quantification, (for the actual study intervention) received. Separate Sub populations will be constructed for participants Randomised to Cohort 1 and Cohort 2 who were in the PK population. [Note: these sub-populations support analyses

Population	Description
	involving PK parameters that can only be derived from a full intensive PK time profile].
Microbiological Modified Per Protocol (Micro-MPP) Population*	All participants randomly assigned to study intervention who receive all planned doses of study intervention and have a Qualifying baseline *E. coli* from a quantitative bacteriological culture of a pre-treatment clean-catch midstream urine specimen.

*The algorithm for determining qualifying *E. coli* based on microbiology laboratory quantitative culture results is provided in the Section 10.8.

Details of additional populations, including targeting non-*E. coli* will be provided in the SAP.

9.3. Statistical Analyses

9.3.1. General Considerations

The estimands for primary endpoint, Microbiological response rate and secondary endpoints safety and PK are included in Section 3. No formal comparisons against Nitrofurantoin are planned as Nitrofurantoin is included in the study only to ensure unbiased reporting of safety events and analysis was designed to demonstrate that the concept behind the novel mechanism of action of GSK3882347 translates into humans. Clinical outcomes, response rates, CCI [redacted] form part of the exploratory analysis. Additional exploratory analysis may be conducted on the microbiology samples according to other uropathogen in combination with the qualifying pathogen and CCI [redacted] to understand the microbiology response rate further depending on the main study results.

In general, data from Cohorts 1 and 2 will be displayed in a single (combined) Table/Figure/Listing; except for selected PK analyses which can only be performed with the full serial time profile.

Microbiological response is the key endpoint used for internal decision-making and additional supportive analyses for internal decision-making may focus on the clinical resolution at the ToC visit, and CCI [redacted] at ToC and Follow Up visit. CCI [redacted]

9.3.2. Primary Endpoint(s)/Estimands(s) Analysis

The analysis of primary endpoint will be done using the Micro-MPP population. The primary endpoint to be estimated is microbiological response at ToC visit in female participants with a qualifying baseline *E.coli*.

Microbiological response at the ToC visit is defined as;

- **Microbiological Success**: Reduction in *E. coli count to* $<10^3$ CFU/mL (no growth) for any *E. coli* identified at ToC visit, without receiving other systemic antimicrobials (rescue medications) prior to ToC.
    - If the baseline urine microbiology quantitative culture has >1 *E.coli* strain present at ≥104 CFU/mL, both E. coli strains must have a reduction to <103 CFU/mL (no growth) to achieve microbiological success.
- **Microbiological Failure**: All other microbiological outcomes (for example but not limited to $\geq 10^3$ CFU/mL for any *E. coli* identified at ToC visit), use of rescue medication prior to ToC, lost to follow-up before ToC, missing/unevaluable samples at ToC, etc).

Use of rescue medications before ToC is captured through the definitions of microbiological response and will be counted as a failures (Composite strategy). Participants who are lost to follow-up prior to ToC, have a missing/unevaluable sample at ToC, discontinue treatment due to any reasons prior to ToC (withdrawal of consent/AEs/missed doses) will be excluded from the analysis and the participant may be replaced at the discretion of the Sponsor. The number and percentage of participants with each category of microbiological response at ToC visit will be summarized, along with 95% CI.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

The secondary endpoints to be evaluated are safety and PK.

Safety Analysis:

Safety analyses will be performed using the safety population. All reported AEs including SAEs, AE related to study intervention, AEs leading to discontinuation of study intervention and/or withdrawal from trial, COVID-19 events etc will be coded using MedDRA and summarized by system organ class and preferred terms.

All AEs, laboratory parameters, ECGs and vital signs for different visits will be reported using appropriate descriptive statistics. GSK core data standards will be followed for all the safety reporting.

Pharmacokinetic Analysis:

Analysis of pharmacokinetic endpoints will be conducted using the pharmacokinetic population.

AUC(0-inf), Cmax, and Tmax from full profiles collected for CCI [redacted] of GSK3882347 on Day 1, AUC(0-24), Cmax, and Tmax from full profiles collected for CCI [redacted] of GSK3882347 on Day 5 & pre-dose Ctau, AUC(0-tau), Observed Accumulation Ratio (Ro) will be determined from plasma concentration data. Urine concentration at 22-24h collection following dose on Day 1 and Day 5, amount excreted in urine (Ae) of unchanged GSK3882347, fraction of the dose excreted in urine (fe), and renal clearance (CLr) will be determined from urine data.

Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum) will be calculated for all pharmacokinetic parameters. In addition, geometric mean, 95% CI, SD on the log scale and % coefficient of variation between participants (CVb) will be provided for log transformed data of PK parameters.

In general, data from Cohorts 1 and 2 will be analysed together; except for selected PK endpoints (AUC(0-inf), Cmax, and Tmax from full profiles collected for CCI of GSK3882347 on Day 1, AUC(0-24), Cmax, and Tmax from full profiles collected for CCI of GSK3882347 on Day 5) which can only be performed with the full serial time profile and hence data will be analysed only for cohort 1 participants.

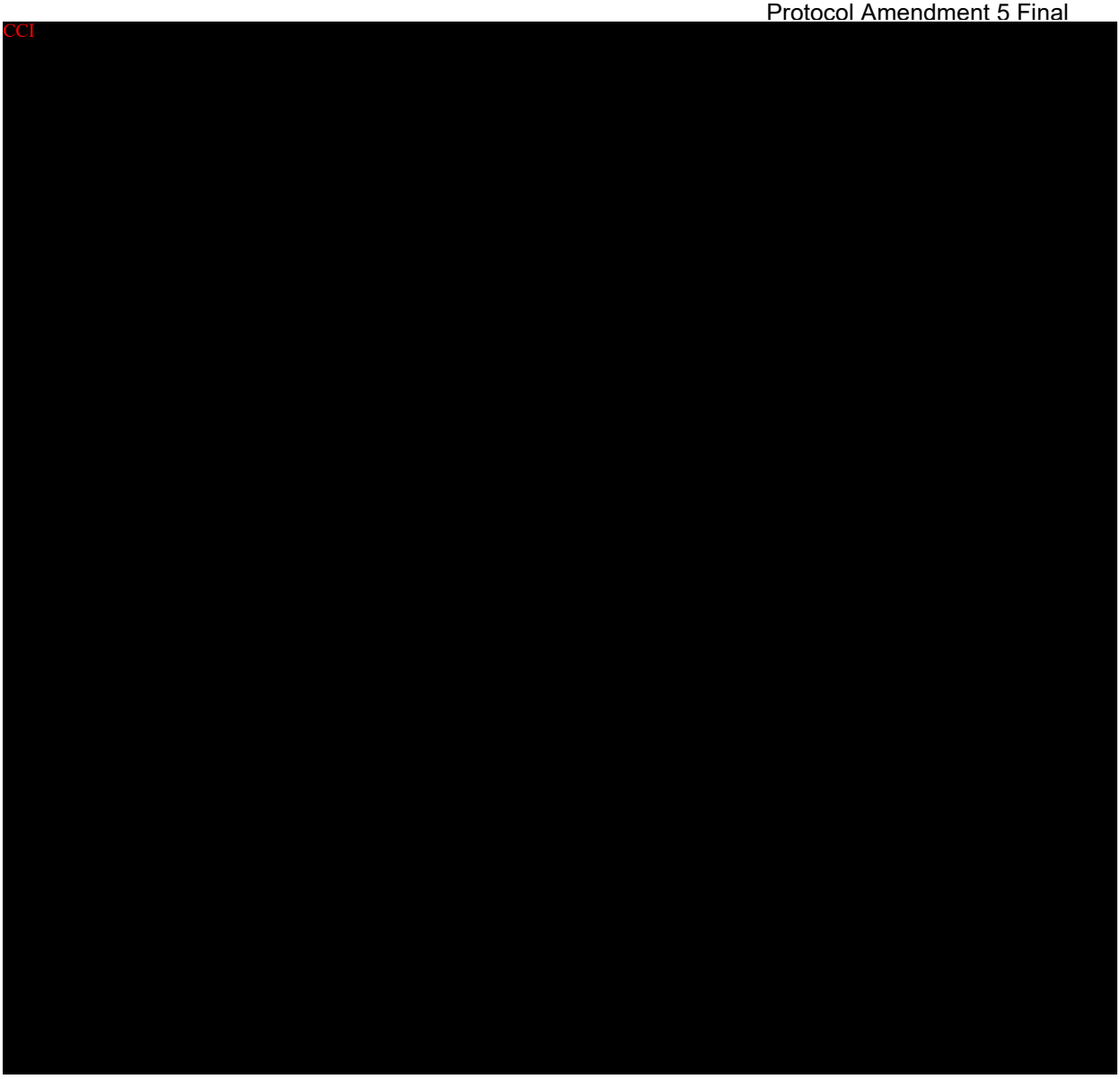
9.3.4. Exploratory Endpoint(s) Analysis

CCI , resolution of clinical symptoms by visits, CCI CCI at ToC and follow-up visits CCI will be analyzed by using appropriate descriptive statistics.

CCI

CCI

[redacted]

CCI


10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human use (ICH) guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protector requirements, where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant.
- Collected samples for the study will be stored as documented in the consent form. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. These additional requirements must be formally communicated to, discussed and agreed with GSK.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

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

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

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research (related and non-related). The investigator or authorized designee will inform each participant of the possibility of further research related or not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research related and not related to the study/disease. Participants who decline further research will tick the corresponding "No" box. There will be separate boxes for further research related and further research non-related, and the participant may choose to provide consent for neither, one, or both of these.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK, third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.5. 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

10.1.5.1. Safety Review Team

- To protect the safety interests of participants, a GSK Safety Review Team will review blinded safety data in stream on a regular basis throughout study conduct. Data reviews will include but are not limited to the following participants:
  - medical monitor, safety team lead, statistician and clinical team lead
- In particular, data will be reviewed by the sponsor for identification of the following events that would potentially contribute to a requirement to halt the study.
  - One (1) or more participants experience a SAE which has a reasonable possibility of being causally related to study intervention.

  - Two (2) or more participants experience a severe or clinically significant non-serious adverse event (based upon investigator judgment) which has a reasonable possibility of relation to study intervention.
  - Three (3) or more participants experience the same adverse event of moderate severity which has a reasonable possibility of relation to study intervention.

- Enrollment will be paused during the review. If a pausing rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.
- Case unblinding may be performed for above reviews if necessary.

10.1.6. 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 Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of 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 clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study participant, as appropriate.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- Under the framework of the Supporting Health for All through Reinvestment (SHARE) initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

- GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data Quality Assurance

- Required participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in corresponding study documentation.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan or equivalent contract research organization (CRO) document.
- 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 a minimum period of 15 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

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

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the central and the local laboratories as identified below.
- Local laboratory/Point of Care results are required for initial participant screening, but otherwise are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or a more immediate safety evaluation. If a local sample is required after the screening visit, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- The addresses of the clinical laboratories in charge of the testing can be found in the “List of Clinical Laboratories and Key Vendors”.

Table 5 Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology#	Platelet count Red Blood Cell (RBC) count Hemoglobin	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular Hemoglobin (MCH) %Reticulocytes (including absolutes)	White Blood Cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Hematocrit			
Clinical Chemistry[1]#	Blood Urea Nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine (including eGFR)	Sodium	Alanine aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase[2]	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal) • Urine protein/creatinine ratio. Urine creatinine and protein values as well as the ratios will be reported in the central lab results.			
Pregnancy testing	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • COVID-19 testing (Lateral flow/rapid turnaround test and a parallel Molecular PCR (in Cohort 1) for screening as per SoA; lateral flow/rapid turnaround test at all other visits as required by local regulation or the Institutional Review Board/Independent Ethics Committee) All study-required laboratory tests will be performed by a central laboratory, with the exception of: • Urinalysis (including drug screen) at screening (excluding microbiology urine sample unless required for non-protocol related SoC) • Hematology and Chemistry at screening • Urine pregnancy test • COVID lateral flow/rapid turnaround test • Suspected Clostridioides difficile infection			

Laboratory Assessments	Parameters

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

 # Point of Care

Point of Care assessments may be used for the following Local laboratory tests on Day -1 (screening visit) only [assessments include Haematology and Clinical Chemistry]

The point of care devices are described in the SRM and may only be used under prior agreement with GSK

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

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

• **Definition of Unsolicited and Solicited AE**
• An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Events NOT Meeting the AE Definition
• 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 signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
• Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

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

10.3.4. Recording, assessment, and Follow-Up of AE, SAE and pregnancies

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form. There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant

AE and SAE Recording
number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. • Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**

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

Assessment of Outcomes

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

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

Follow-up of AE, SAE, pregnancies and any other events of interest

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

After the initial AE/SAE/pregnancy, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until the study follow up visit, as set out in the SoA, or until the participant is lost to follow-up.

Follow-up during the study

AEs 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 study follow up visit, as set out in the SoA.

Follow-up of AE, SAE, pregnancies and any other events of interest
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 paper pregnancy follow-up report/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 should 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 the Section 10.3.5.

Updating of SAE and pregnancy information after removal of write access to the participant's eCRF
• When additional SAE, or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the study contact for reporting SAEs (see Section 8.3.3).

10.3.5. Reporting of SAE and pregnancies to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool

SAE Reporting to GSK via Electronic Data Collection Tool
has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone. • If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned CA via the national spontaneous reporting system. These will be classified as spontaneous ICSRs. • Contacts for SAE reporting can be found in the SRM and Section 8.3.7

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • In rare circumstances and in the absence of 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 time frames. • Contacts for SAE reporting can be found in the SRM and Section 8.3.7

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
- **Note:** Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

   a) Documented hysterectomy

   b) Documented bilateral salpingectomy

   c) Documented bilateral oophorectomy

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

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

2. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

During the study participants are asked to consent and adhere to the study lifestyle restrictions by adhering to abstinence of sexual activity through the study to prevent exacerbation of clinical and microbiological outcomes associated with their infection.

However, the following guidance on contraception requirements should still be discussed with the participant around acceptable contraceptive requirements.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY IF PARTICPANT IS NOT ABLE TO ABSTAIN 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
Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation • oral • injectable

• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. 5 Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. 6 **Male condoms must be used in addition to hormonal contraception.** If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DEOXYRIBONUCLEIC ACID (DNA)

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for germline DNA analysis
- DNA samples will be used for research related to GSK3882347, nitrofurantoin or UTI and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3882347 or study interventions of this drug class, and UTI. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK3882347 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained while research on GSK3882347 (or study interventions of this class) or UTI continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

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

Phase 1 liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology

Phase 1 Liver Chemistry Stopping Criteria and Required Follow Up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN

If ALT≥3xULN AND total bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) OR international normalized ratio (INR)>1.5, Report as an SAE.</td></tr>
<tr><th colspan="3">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event form, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments as described in the Follow Up Assessment column.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING)

MONITORING:

If ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis within 3 days of last dose[4]
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin.
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form
• Record use of concomitant medications on the concomitant medications CRF page including acetaminophen, herbal remedies, recreational drugs and other over the counter medications.
• Record alcohol use on the liver event alcohol intake form

If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5 obtain the following in addition to the assessments listed above:</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
If ALT≥3xULN AND total bilirubin < 2xULN and INR ≤1.5: • Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline **RESTART/RECHALLENGE** **Do not restart/rechallenge** participant with study intervention since **not allowed per protocol;** continue participant in the study for any protocol specified follow up assessments.	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout). • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete liver imaging form. • Liver biopsy may be considered and discussed with local specialists if available for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and total bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE**(excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HbsAg and HBcAb; hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody
4. 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 CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

10.7. Appendix 7: Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment

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

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

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

Note: Adult DMID toxicity criteria will be applied for all laboratory parameters, with the exception of serum creatinine adolescent laboratory data, which will be assessed using pediatric DMID toxicity criteria. The DMID pediatric toxicity table may be accessed at https://www.niaid.nih.gov/sites/default/files/dmidpedtox.pdf.

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

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

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

Rx=therapy; ULN=upper limit of normal.

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

Rx=therapy; ULN=upper limit of normal.

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

ULN=upper limit of normal.

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

HPF=high-power field; RBC=red blood cells.

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

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

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

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

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

IV=intravenous.

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

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

ADL=activities of daily living.

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

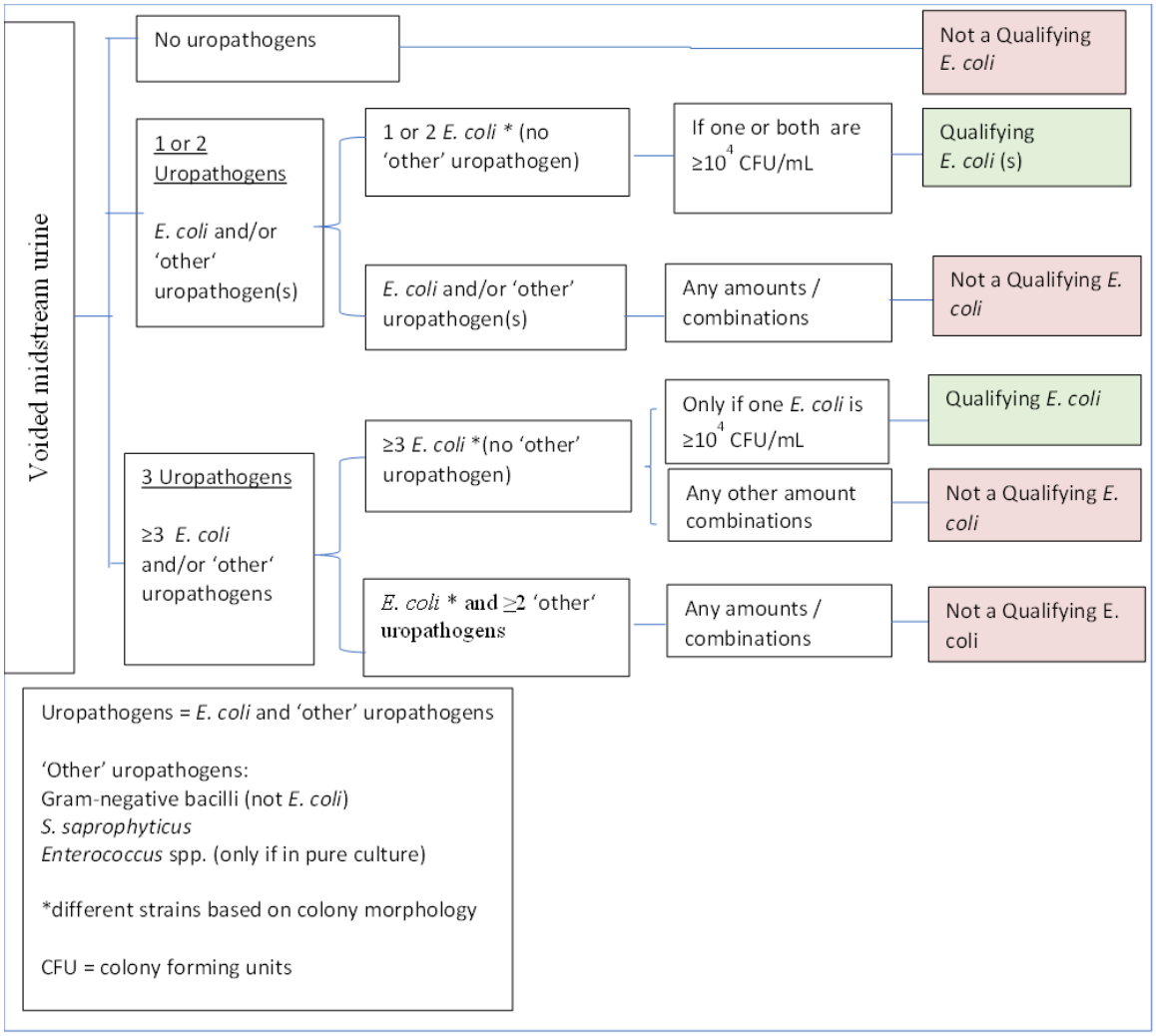
N/A=not applicable.

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

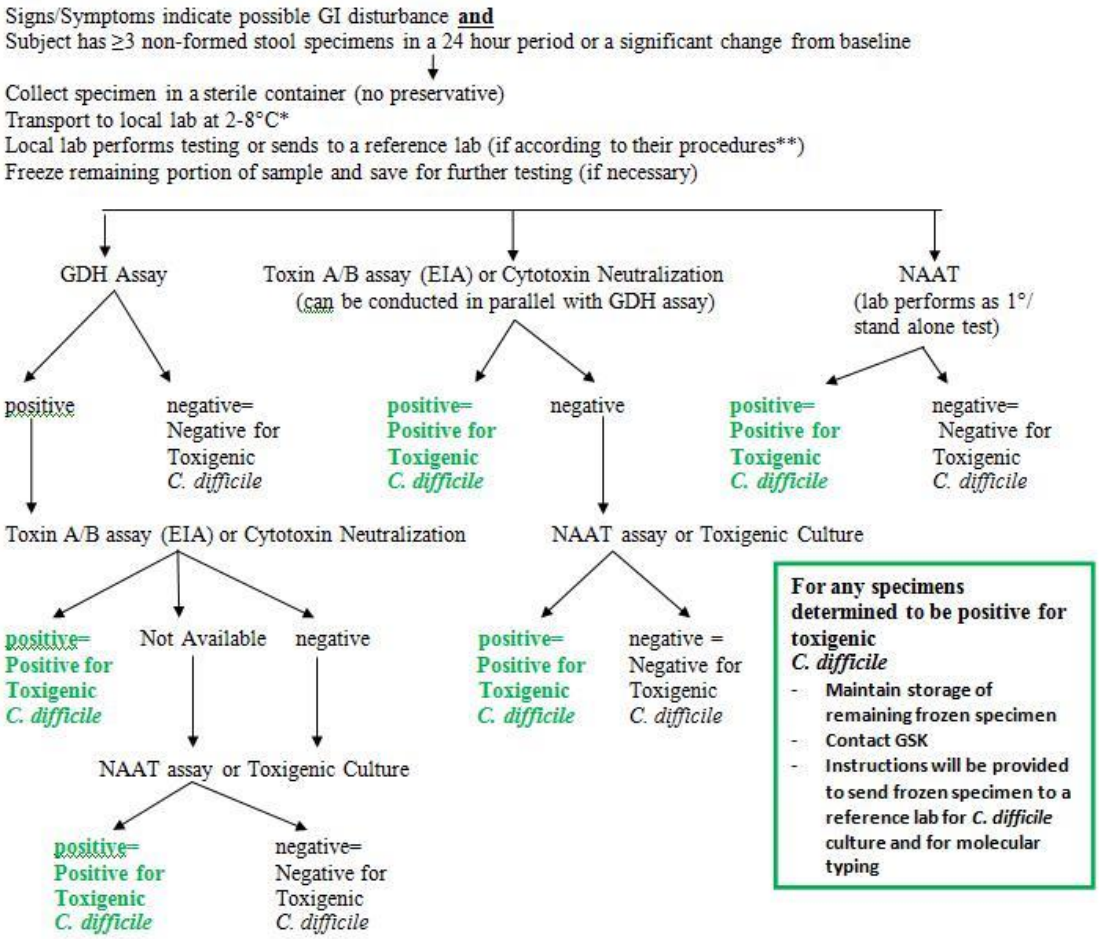
10.8. Appendix 8: Algorithm for Determining Qualifying *E. coli* Pathogen

In addition to other criteria defined in the Inclusion Criteria, only participants with a qualifying *E. coli* uropathogen at Baseline from a quantitative bacteriology culture of a pre-treatment cleancatch midstream urine specimen will be included in the Microbiological (Micro-MPP) Population. Please refer to the analysis plan for additional details. The algorithm for determining qualifying *E. coli* uropathogen based on microbiology laboratory quantitative culture results is provided below.

Figure 3 Algorithm for qualifying *E. coli* Pathogen



10.9. Appendix 9: Algorithm for Detecting Suspected *C. difficile* infection



*If processing and testing cannot be performed within 24 hours, the specimen should be frozen immediately after collection.
**If specimen is sent to a reference laboratory, the procedures to be ordered should follow the same algorithm above.
GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test

10.10. Appendix 10: Abbreviations, Definition of Terms and Trademarks

ACE	Angiotensin-converting enzyme
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
Ae	Amount Excreted in Urine
AIDS	Acquired Immuno Deficiency Syndrome
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AST	Antimicrobial Susceptibility Testing
CCI [redacted]	
BCRP	Breast cancer resistance protein
BID	Bis In Die (Twice A Day)
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C. difficile	Clostridioides difficile
CA	Competent Authority
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CCI [redacted]	
CCI [redacted]	
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CCI [redacted]	
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
CV	Coefficient of Variation
CVb	Coefficient of Variation Between Subjects
CYP	Cytochrome P450 3A4
CCI [redacted]	
DDI	Drug-drug Interaction
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid

E. coli	Escherichia coli
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Early discontinuation
eGFR	Estimated Glomerular Filtration Rate
EIA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
CCI	[redacted]
FeV_1	Forced Expiratory Volume in 1 second
FimH	type 1 fimbrial adhesin A mannose-specific adhesin located on the tip of type 1 fimbriae of *E. coli*
FSH	Follicle-stimulating Hormone
FTIH	First Time in Human
G6PD	Glucose-6-phosphate Dehydrogenase
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GDH	Glutamate Dehydrogenase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HAI	Hemagglutinin Inhibition
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HPF	High Power Field
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IP	Investigational Product
IRT	Interactive Response Technology
ITT	Intent to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IV	Intravenous
IV/IVT	In Vivo/In Vitro
Kg	Kilogram

L	Liter
LAM	Lactational Amenorrhea Method
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI response	Microbiological Response
Micro-MPP	Microbiological Modified Per Protocol
mL	Millilitre
Msec	Millisecond
NAAT	Nucleic Acid Amplification Test
NOAEL	No-observed-adverse-effect Level
NSAID	Non-steroidal anti-inflammatory drugs
OAT	Organic anion transporter
PBPK	Physiologically Based Pharmacokinetic
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
POC	Point of Care
PoM	Proof-of-Mechanism
CCI	CCI
QRS	ECG waveform
QT	ECG waveform
QTc	Corrected QT; The measure of time between the start of the Q Wave and the end of the T Wave
QTcF	Corrected QT Interval Using Fridericia's Formula
QTL	Quality Tolerance Limits
RBC	Red Blood Cell
RNA	Ribonucleic Acid
Ro	Observed Accumulation Ratio
Rx	Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SD	Standard Deviation
SHARE Initiative	Supporting Health for All through Reinvestment Initiative
SoA	Schedule of Activities
SoC	Standard of Care
SRM	Study Reference Manual
SUSARs	Suspected Unexpected Serious Adverse Reactions
CCI	
ToC	Test of Cure
TTS	Technical Terms of Supply
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
WBC	White Blood Cell

Term	Definition
ADR	An AE where a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. In the context of a clinical trial, an ADR can be serious or nonserious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.
Background treatment	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard of care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a double-blind study, the participant, the investigator, and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g., double-blinded consistency lots which are open with respect to the control group.
Caregiver	A “caregiver” is someone who: • lives in the close surroundings of a participant and has a continuous caring role or • has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant’s compliance with protocol-specified procedures.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (e.g., by a dated signature or by

Term	Definition
	generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Challenge agent	A product given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.
Child in care	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government, or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Co-administered product	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition that is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Comparator	Any product used as a reference (including placebo, marketed product, GSK, or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Decentralized trial platform	A digital engagement technology allowing for the remote delivery and access to trials for participants, sites, and sponsors.
DFP shipments	Home pickup of collected biological specimens, or pickup and return of unused/partially used/expired trial materials for return to investigator site.
DTP shipments	Shipping of IMP, laboratory kits, devices, etc., to the participant's residence under secure and controlled conditions.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Intercurrent event	Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.
Intervention number	A number identifying the intervention assigned to a participant, according to intervention allocation.
Investigational Product or Investigational Medicinal Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from

Term	Definition
	the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
LAR	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
LSLV	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Medicinal products used to assess endpoints	A product given to the participant in a clinical trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Participant identifier	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
PGx	The ICH E15 Guidance for Industry defines PGx as "the study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of PGx, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g., mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or

Term	Definition
	genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (PK, safety, efficacy, or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not PGx.
Primary completion date	This is the date that the final participant in the study was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In other words, Primary Completion Achieved is the date of the last contact with the participant when data has been collected/intervention done for the purpose of data collection for analysis of all primary endpoints. In the case of clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. This date may occur prior to the study end or be the same date as the study end milestone.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	A visit conducted in the place other than the study site.
Rescue medication	Medicine(s) identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the participant, or to manage an emergency situation.
Self-contained study	Study with objectives not linked to the data of another study.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.

Term	Definition
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Subcohort	A group of participants for whom specific study procedures are planned as compared with other participants or a group of participants who share a common characteristic (e.g., ages, vaccination schedule) at the time of enrollment.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

TRADEMARK INFORMATION

Trademarks of the GSK group of companies
None

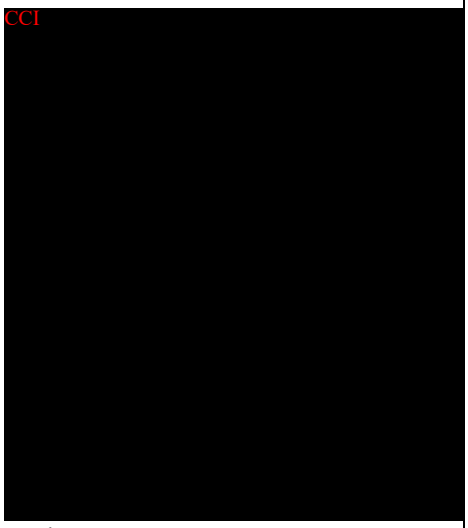
Trademarks not owned by the GSK group of companies
Macrobid

10.11. Appendix 11: Protocol Amendment History

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

Amendment 4 05 May 2023

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities: Cohort 2	Footnote added to describe home visits for outpatient visits	Allowance of home visits (with prior agreement from GSK) to ease scheduling restrictions at sites
1.3 Schedule of Activities Cohort 1 and Cohort 2	Footnote added stating baseline data will be collected at pre dose on Day 1 (except for triplicate ECG which uses Day -1 screening) Extension of screening lab results to up to 24hr (plus 6 hrs) Footnote added to reference Point of Care (POC) devices at screening	Clarification of baseline timepoint, extension of lab result turnaround time and allowance of POC devices at screening following prior agreement with GSK to ease site and patient burden at the screening visit
1.3 Schedule of Activities	Urine and Plasma PK predose Cohort 1 added to main SOA	To align Main SOA with detailed PK sampling SOA
1.3.1. Cohort 1: Intensive PK Profiling During an Inpatient Intervention Period	Under Urine pregnancy test Added: (for women of childbearing potential)	Added text is to clarify that the use of pregnancy testing is for women of childbearing potential. Pregnancy testing is not required in women that are confirmed to be of nonchildbearing potential.
1.3.2. Cohort 2 Reduced PK Sampling During an Outpatient Intervention Period	Under Urine pregnancy test Added: (for women of childbearing potential)	Added text is to clarify that the use of pregnancy testing is for women of childbearing potential. Pregnancy testing is not required in women that are confirmed to

Section # and Name	Description of Change	Brief Rationale
		be of nonchildbearing potential.
2.3.1 Risk Assessment Reproductive toxicity	Update of wording regards animal reproductive studies	Animal reproductive studies now complete.
3.Objectives and Endpoints and/or Estimands	Primary estimand on subjects who completed the planned course of treatment	Interest lies in the treatment effect of participants who completed treatment to establish proof of mechanism
3.Objectives and Endpoints	Secondary and exploratory objectives for PK updated	Due to recruitment challenges in Cohort 1, there is a risk that the following PK parameter analysis will not be able to be conducted. The following PK parameters, which can only be measured calculated from data generated in Cohort 1, have therefore been moved to exploratory. CCI  <u>Urine</u> • Amount excreted in urine (Ae) of unchanged GSK3882347, fraction of the dose excreted in urine (fe), and renal clearance (CLr)
5.1 Inclusion criteria	Inclusion criteria 3 updated to increase Leukocyte esterase threshold to 2+ Wording now 'The	To help increase the potential for participants to have an infection that meets the current defined evaluability criteria.

Section # and Name	Description of Change	Brief Rationale
	participant has nitrite OR pyuria (≥10 WBC/mm^3, OR >5 WBC/HPF OR the presence of 2+ leukocyte esterase) from a pre-treatment clean-catch midstream urine sample based on local laboratory procedures.'	
5.2 Exclusion criteria	Exclusion criteria 11 updated to reference eGFR	Exclusion criteria 11 has referenced the units associated with estimated Glomerular Filtration Rate (eGFR= ml/min/ 1.73m2) but has incorrectly associated these units with creatinine clearance (which has a standard value in ml/min). Therefore, the term creatinine clearance has been updated to eGFR. For consistency between sites, the equation for the calculation of the eGFR.
5.2 Exclusion criteria	Exclusion criteria 11 updated to remove requirement for assessment of urine albumin:creatinine ratio at screening.	Assessment of urine albumin:creatinine ratio has been removed as a requirement at screening. Participants with a history of proteinuria are excluded, as per exclusion criteria 28. Assessment of urine protein:creatinine ratio will continue to be performed by the central labs at Day 1 predose and all further laboratory assessment timepoints specified in the SoA table.
5.2 Exclusion criteria	Exclusion criteria 26 updated to allow medical use of marijuana	Marijuana use is legal in some US states and therefore is not classed as a substance of abuse.

Section # and Name	Description of Change	Brief Rationale
	'Substance abuse: Active substance abuse or a history of substance abuse (in the opinion of the Principal Investigator) within 6 months prior to the initial Screening visit. Note that *documented* medical use of marijuana or occasional recreational use of marijuana is permitted	
5.2 Exclusion criteria	Exclusion criteria 28 updated to reference proteinuria	Exclusion criteria 28 has been updated to clarify that a history of significant renal conditions includes a history of significant or chronic proteinuria.
5.2 Exclusion criteria	Exclusion criteria 30 Correction of criteria from 'must', to 'does not' The participant **does not** agree to adhere to the concomitant therapy restrictions as described in Section 6.8.2 from the Screening Visit through to the Follow Up Visit.	Word change of criteria to correct direction of exclusion
5.4 Screen Failures	Addition of following wording Scheduling of Day 1 visit falls outside of 24hrs however participant will remain within 96 hours of symptom onset.	To aid scheduling of day 1 visits at site for patients as long as they remain to meet all entry criteria
6.8.2 Prohibited Meds	Text updated to the	Correction of grammar

Section # and Name	Description of Change	Brief Rationale
	following Known nephrotoxic medications (e.g. ACE inhibitors, Angiotensin receptor blockers) and regular NSAID use should be avoided	
8.2.2 Vital Signs	Flexibility to allow semi- supine or seated positions for vital sign assessment	To allow sites to adhere to their local standard procedures
8.9 Administrative and general baseline procedures	New section added outlining justification of collection of demographic information and use of third parties	Mandated text included due to new GSK process to justify demographic collection and transparency of third-party use.
9.2 Analysis Sets	Rename ITT population to Exposed and group by actual treatment rather than randomised	Interest lies in treatment effect of actual treatment received. This population is used for listings
9.2 Analysis Sets	Update definition of micro-ITT to require “all planned doses” rather than “at least 1 dose” and rename as Micro-MPP.	Interest lies in treatment effect following 5 days dosing
CCI [redacted]		
Appendix 2	Clinical Chemistry updated to reference	Exclusion criteria 11 has the values of estimated Glomerular Filtration Rate (eGFR= ml/min/

Section # and Name	Description of Change	Brief Rationale
	eGFR	1.73m2) but has incorrectly stated creatinine clearance (which has a standard value in ml/min). Therefore, the term creatinine clearance has been adjusted to eGFR, and the clinical chemistry list updated to reflect this adjustment.
Appendix 10.2. Clinical Local Laboratory Tests	Guidance on POC assessment at screening	Allowance of POC devices at screening following prior agreement with GSK to ease site and patient burden at the screening visit
Appendix 11 Acronym table	eGFR and POC added	New acronyms
Appendix 12: Protocol Amendment History-PA3 Summary Table	Updated the word "and" to "or" in the text Updated definition of pyuria from >15WBC/HPF **and** presence of 3+ /large leukocyte esterase to ≥10WBC/mm3 or >5WBC/ HPF **or** presence of leukocyte esterase.	For Clarification
11 References	Reference for CKD-EPI added	Reference for equations to calculate eGFR

Amendment 3 07 Oct 2022

Overall Rationale for the Amendment: The following updates were made to reduce patient burden within this study, expand enrollment criteria and administrative changes.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) Cohort 1 and Cohort 2 8. Study Assessments and Procedures	Pre-screen ICF available for local urinalysis (dipstick) and pregnancy test. Added pre-screening language for clarification in the SoA tables and Section 8	A pre-screen ICF was added to obtain consent for the collection of a urine sample to support study enrollment (specifically inclusion #3)
2.3.1 Risk Assessment	Reproductive toxicity added as a potential risk and CYP3A4 induction risk.	This addition is not based on any new emerging safety information. Instead, it is to clearly state the unknown risk of drug exposure in pregnant women in this section and align risk language with wording already entered in the protocol (Section 10.4) and study documents. Pre-existing protocol inclusion criteria for WOCBP including contraceptive guidance and pregnancy testing remain in place. Changes added to expand the required duration of contraception use for WOCBP using hormonal contraceptives (due to potential CYP3A4 induction risk) and to clearly state in this section that double barrier contraception required as already stated in Section 10.4).
5.1 Inclusion Criteria #2	Updated the onset of clinical signs and symptoms from ≤72 hours to <96 hours	To allow participants further flexibility to enroll within the study.
5.1 Inclusion Criteria #3 8.1.2 Microbiology Outcome and Response	Updated definition of pyuria from >15WBC/HPF or presence of 3+ /large leukocyte esterase to ≥10WBC/mm^3 or >5WBC/ HPF or	To expand definition of pyuria and therefore further participant inclusion into the study.

Section # and Name	Description of Change	Brief Rationale
	presence of leukocyte esterase.	
5.1 Inclusion Criteria #5	Expanded and added clarification to contraceptive requirements for WOCBP using hormonal contraceptives	This amendment is not based on any new emerging safety information. Instead, it is to align with the updated risk benefit section and align with wording already entered in the protocol (Section 10.4) and study documents. Pre-existing protocol inclusion criteria for WOCBP including contraceptive guidance and pregnancy testing remain in place. Changes added to expand the required duration of contraception use for WOCBP using hormonal contraceptives (due to potential CYP3A4 induction risk) and to clearly state in this section that double barrier contraception required as already stated in Section 10.4).
5.2. Exclusion Criteria #29	Prior/Concomitant Therapy: updated antimicrobials or systemic antifungals used within 4 weeks to within 1 week of study entry.	Changes needed to align with the Concomitant Therapy Section (6.8.2) of the protocol. Dalbavancin or oritavancin exclusion changed to ten weeks before study start due to the long half-life compared to other antimicrobials.
6.8.2 Prohibited Medication and Non-Drug Therapies	Updated antimicrobials or systemic antifungals used within 4 weeks to within 1 week of study entry with the exception of dalbavancin and oritavancin.	It was determined that a one week period prior to study entry is sufficient. Dalbavancin or oritavancin exclusion changed to ten weeks before entry due to longer half-life values compared to other antimicrobials.

Section # and Name	Description of Change	Brief Rationale
	Removed restrictions on substrates of BCRP and OATP1B1 (e.g. statins)	PBPK modelling has superseded static equations which initially flagged a potential for GSK3882347 to perpetrate DDIs with substrates of BCRP and OATP1B1. The PBPK model has since confirmed there is a low risk of clinically meaningful DDIs with substrates of these transporters.
8 Study Assessments and Procedures 1.3 Schedule of Activities (SoA) Cohort 1 and Cohort 2	Addition of potential e-consent	To allow participants further flexibility to enroll within the study.
Various Sections	Minor editorial updates	For clarification

Amendment 2 24Feb2022

Section # and Name	Description of Change	Brief Rationale
2.3.1. Risk Assessment	Summary of nonclinical findings and mitigation strategy added to the Risk Assessment table.	Pre-clinical risk associated with renal changes in rats identified as a potential risk of clinical significance.
5.2. Exclusion Criteria #11	Creatinine clearance value changed from <60 mL/min/1.73m^2 to <90 mL/min/1.73m^2.	Pre-clinical risk associated with renal changes in rats identified.
5.2. Exclusion Criteria #28	Criteria updated to include a specific list of conditions that could be exclusionary.	List added to emphasize the desire for relatively healthy study population.
5.2. Exclusion Criteria #30	Reference to the relevant protocol section added, Baseline Visit updated to Screening Visit and ToC changes to Follow up visit.	Changes needed for clarity and to align with the Concomitant Therapy Section (6.8.2) of the protocol.

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria #37	Deleted.	Changes to Exclusion #30 made #37 redundant.
6.3. Measures to Minimize Bias: Randomization and Blinding	Sentence added regarding the use of an unblinded team for the purpose of the Interim Analysis.	Addition to emphasize the use of an internal unblinded team to review and conduct interim analysis.
6.8 Concomitant Therapy	Section restructured and potential drug-drug interactions added.	Restructured for clarity, additional potential drug-drug interaction to reflect FDA feedback and specific details around nephrotoxic drugs added.
New Section: 8.2.4.2 Management of participants with changes in serum creatinine	Section 8.2.4.2 added.	Section added to ensure appropriate monitoring of serum creatinine changes.
CCI [redacted]		
10.2. Appendix 2: Clinical Laboratory Tests Table 3 Protocol-required Safety Laboratory Tests	Additional expected results added to table and text for the collection of a SoC microbiology urine sample at screening added.	Lab appendix updated to better reflect laboratory testing originally included during set-up of assessments (e.g., addition of absolute value included and reported in central lab standard panels and calculations for serum and urine creatinine) and to clarify a microbiology urine sample at screening can be obtained as part of SoC.
10.7.2. Procedures During COVID-19 Pandemic	Language added to describe circumstances and procedures for alternate COVID-19 testing.	Due to potential inconsistencies in availability of rapid antigen tests kits (e.g., rise in variants creating high demand/low supply of kits) alternate testing measures were added for these types of circumstances.
Various locations	Clerical updates.	Minor corrections to clean document.

Amendment 1 17-Dec-2021

Overall Rationale for the Amendment: An inclusion and exclusion criterion were modified to enhance study recruitment and the microbiological response definitions were clarified based on FDA advice.

Section # and Name	Description of Change	Brief Rationale
1.3.2. Cohort Reduced PK Sampling During an Outpatient Intervention Period SoA Table	UTI Clinical Signs and Symptom Score Assessment at Post Dose on Day 1 was removed.	The assessment at this timepoint was added in error.
5.1. Inclusion Criteria	Inclusion 3 edited to permit participant inclusion with nitrite *or* pyuria positive urinalysis.	Edit to inclusion criteria to expand the potential participant involvement and number of evaluable participants in the study considering the sensitivities of the assays. Wording 'Nitrite AND Pyuria' replaced with Nitrite **OR** Pyuria'.
CCI [redacted]		
9.3.2. Primary Endpoint(s)/Estimands(s) Analysis	Definition of microbiological response clarified.	Based on FDA advice, the definitions for microbiological response were revised to clarify that a reduction in any/all *E. coli* counts at the ToC visit determine the microbiological response.
Various locations	Typo and formatting issues corrected.	Minor corrections to clean document.

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