TITLE PAGE

Protocol Title: A Double-Blind Randomized, Placebo-Controlled, Single and Repeated Oral Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics (including food effect) of GSK3882347 in Healthy Participants

Protocol Number: 212148

Compound Number:	GSK3882347

Study Phase: Phase 1

Short Title: Safety, tolerability and pharmacokinetic investigation of GSK3882347 in healthy participants

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): EudraCT No. 2020-000680-23

Approval Date: 21-OCT-2020

SPONSOR SIGNATORY:

PPD

PPD

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Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 3	*21-Oct-2020*	*2019N400733_03*
Amendment 2	*10-Jul-2020*	*2019N400733_02*
Amendment 1	*02-Jun-2020*	*2019N400733_01*
Original Protocol	*05 -Nov-2019*	*2019N400733_00*

Amendment 3: 21-OCT-2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: This amendment is to allow for additional blood samples to be taken from selected cohorts in order to evaluate an *in vitro* CYP3A4 induction flag. Plasma derived from whole blood will be analysed for changes in 4β-hydroxycholesterol and cholesterol ratio as a potential *in vivo* marker of CYP3A4 enzyme activity at baseline and following repeat administration of GSK3882347.

Section # and Name	Description of Change	Brief Rationale
1.3 SoA (Table 3 and Table 4)	Addition of 4β-hydroxycholesterol sampling in plasma.	To evaluate CYP3A4 induction within Part 2 of the study following repeat administration of GSK3882347.
1.3 SoA (Table 4)	Continuous cardiac monitoring will be approximately 24 hours on Days 1 and 7 (part 2 only) in both parts.	A line has been added to the table for this activity. There was an omission of the stop time included in Table 4 where a "X" should have been marked to represent the end of this collection period.
1.3 SoA (Table 1 to Table 4)	Updated language for stool sample collections/assessments. Added timing of collection window.	Clarification of stool type assessment will be performed on all bowel movements while in the clinical unit. Clarification stool collection can be up to 72 hours (3 days) prior to required sample.
3 Objectives and Endpoints	Addition of exploratory objective to assess the potential effect of repeat doses of GSK3882347 on Cytochrome P450 3A4 (CYP3A4) enzyme activity.	To evaluate CYP3A4 induction within Part 2 of the study.
4.2 Scientific Rationale for Study Design	Addition of rationale to use plasma marker to explore CYP3A4 induction.	GSK3882347A was shown be a moderate inducer of CYP3A4 *in vitro* and has the potential to contribute to DDIs with CYP3A4 substrates, including oral contraceptives.
5.3.1 Meals and Dietary Restrictions	Clarification of meals and snacks.	Standardized meals/food practices including snacks and beverages provided by the clinical unit.
6.5.2. Prohibited Medications	Added prohibited medications.	Prohibited medications which are substrates of CYP3A4 and sensitive to induction are not permitted.
8.6 Plasma Sample for CYP3A4 Enzyme Activity	Addition of 4β-hydroxycholesterol sample collection.	Collection details.

Section # and Name	Description of Change	Brief Rationale
Appendix 9 COVID-19 Appendix (Section 10.9.3)	Additions of Protocol Defined Procedures/Visits.	As COVID-19 mitigation strategies.
Appendix 10 Protocol Amendment History	Relocation of Amendment 2.	Amendment 2 moved to the Amendment History.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Double-Blind Randomized, Placebo-Controlled, Single and Repeated Oral Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics (including food effect) of GSK3882347 in Healthy Participants

Short Title: Safety, tolerability and pharmacokinetic investigation of GSK3882347 in healthy participants

Rationale:

GSK3882347 is a potent and specific competitive antagonist of the *Escherichia coli* type 1 pilus adhesin molecule FimH which is being developed as an antibiotic-sparing treatment for uncomplicated urinary tract infections. The goal of this study is to evaluate the safety, tolerability and pharmacokinetic properties (including food effect) of GSK3882347 following oral administration of single and repeat doses in healthy adult participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3882347 following oral administration of single and repeat doses in healthy adult participants • To evaluate the pharmacokinetics of GSK3882347 in plasma and urine following oral administration of single and repeat doses in healthy adult participants	• Occurrence of adverse events (AEs) and treatment related AEs • Occurrence of clinically significant changes in vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings • Single dose (plasma): AUC(0-24), AUC(0-t), AUC(0-inf), Cmax, C24h, tmax, tlag and t1/2 of GSK3882347, as data permit • Repeat dose (plasma): AUC(0-tau), Cmax, tmax and Ctau of GSK3882347, as data permit • Urine concentration at 22-24h collection time-point • Amount excreted in urine (Ae) of unchanged GSK3882347, fraction of the dose excreted in urine (fe) and renal clearance (CLr), as data permit

Objectives	Endpoints
Secondary	
• To further evaluate the pharmacokinetics of GSK3882347 in plasma • To examine dose proportionality of GSK3882347 following oral administration of single and repeat doses in healthy adult participants • To evaluate the extent of accumulation, time invariance, and achievement of steady-state of GSK3882347 following oral administration of single and repeat doses in healthy adult participants	• Single dose (plasma): AUC(0-12), C12h,CL/F, Vd/F and MRT of GSK3882347, as data permit • Repeat dose (plasma): AUC(0-12) and C12h of GSK3882347, as data permit • AUC(0-inf) and Cmax for single dose and AUC(0-tau) and Cmax for repeat dose, as data permit • Ro (accumulation ratio) using AUC(0-tau) for repeat dose, as data permit • Time invariance using AUC(0-tau) (repeat dose) and AUC(0-inf) (single dose) • Achievement of steady-state (Ctau collected on multiple days)
• To evaluate the effect of food on pharmacokinetics of GSK3882347 following oral administration of single dose in healthy adult participants	• AUC(0-24), AUC(0-t), AUC(0-inf), C24h, Cmax, tmax and tlag, as data permit

Overall Design:

This is a two-part phase I, first-time-in-human (FTIH), randomized, double-blind, single-center, placebo-controlled, dose-escalation study to determine the safety, tolerability and pharmacokinetic profile of GSK3882347 following oral administration of single (Part 1) and repeat doses (Part 2) in healthy adult men and women of non-child bearing potential (WONCBP). Part 1 will consist of two cohorts with up to a four-period cross-over. The food effect evaluation will be conducted in the last period (Period 4) in only one of the cohorts based on the observed human pharmacokinetics.

During Parts 1 and 2, participants who met the criteria for study entry will be assigned to the current dose level and randomized to receive GSK3882347 or placebo before administration of study intervention on Day 1.

Dose escalation will be conducted only if it is supported by safety, tolerability and pharmacokinetic results from the preceding dose level(s). This is the first administration of GSK3882347 in humans; therefore, preliminary safety, tolerability and pharmacokinetic results will be reviewed internally at GSK in conjunction with the study site and study design adjustments may be made based on emerging data from each dose cohort. The point at which Part 2 is initiated can be modified based on the emerging safety, tolerability and pharmacokinetic data from Part 1.

Study schematic is provided in Figure 1

This is a two-part phase I, first-time-in-human (FTIH), randomized, double-blind, single-center, placebo-controlled, dose-escalation study to determine the safety, tolerability and pharmacokinetic profile of GSK3882347 following oral administration of single (Part 1) and repeat doses (Part 2) of GSK3882347 in healthy adult men and WONCBP.

Part 1 is a cross-over design single ascending dose study in 2 cohorts with a maximum of 4 periods per cohort that is participant and investigator blinded. The effect of food on a single oral dose of GSK3882347 may be evaluated as period 4 of Part 1. The dose of GSK3882347 will be selected based on the review of the ongoing data from the prior single ascending doses and predicted to be within the predicted therapeutic range.

Part 2 is a multiple ascending dose study in a maximum of 4 cohorts that is participant and investigator blinded.

Number of Participants:

Approximately 56 randomized participants will be enrolled for the entire study.

For Part 1, approximately 16 healthy adult participants will be enrolled with a minimum of eight participants each in Cohorts 1 and 2, where each cohort may participate in up to four periods. In each cohort, a minimum of six participants will be assigned to active treatment and a minimum of two participants will be assigned to placebo according to a randomization schedule prepared prior to the start of the study.

For Part 2, approximately 40 healthy adult participants will be enrolled with a minimum of ten participants in each of the four planned cohorts. In each cohort, a minimum of eight participants will be randomized to receive active treatment and a minimum of two participants will be randomized to receive placebo according to a randomization schedule prepared prior to the start of the study.

Part 1 is planned to include six dose levels. Up to two additional doses (1 per cohort) may be evaluated to further understand the study intervention. Part 2 is planned to include four dose levels.

If participants prematurely discontinue the study in Parts 1 and 2, they may be replaced at the discretion of the sponsor Medical Monitor in consultation with the Principal Investigator. The replacement participants will be assigned to the same treatment sequence, starting where the prior participant prematurely discontinued. Previously administered doses will not be repeated by replacement participants if dose escalation criteria are met.

Sample Size Determination and evaluable subjects are described in Section 9.2.

Intervention Groups and Duration:

Part 1: Single Dose Escalation and Food Effect in Healthy Adult Participants

Part 1 will consist of a maximum of four periods in a cross-over design conducted in two separate cohorts of eight healthy participants. Each of these two cohorts may participate in a maximum of four periods and will receive three doses (escalations or reductions) of GSK3882347 and a potential assessment of food effect. The food effect evaluation will be conducted in only one of the cohorts which will be selected based on the observed human pharmacokinetics. The planned starting GSK3882347 dose in Part 1 is 50 mg administered as a single oral dose. The dose is planned to increase in subsequent cohorts to 150, 250, 500, 750, and 900 mg. In each escalating dose level, six participants will be randomized to GSK3882347 and two participants will be randomized to placebo.

Participants who meet the criteria for study entry will be assigned to a cohort and randomized to receive GSK3882347 or placebo in a 3:1 ratio before administration of study intervention on Day 1 in Part 1. As a safety precaution, cohorts 1 and 2 will be split into two sub-cohorts to allow sentinel dosing. At each dose level (Cohort 1 and 2), the first two participants will receive either GSK3882347 or placebo (one active and one placebo). Dosing of the remaining six participants (five active and one placebo) in that cohort will occur at least 24 hours later based on review of the safety data (e.g. vital signs, ECGs, clinical laboratory results and adverse events) by the Principal Investigator and sponsor Medical Monitor from all sub-cohorts of sentinel participants. Doses are planned to escalate in a sequential fashion contingent on the safety, tolerability and pharmacokinetic profile of a minimum of four participants who received active treatment in the previous cohort. Dose escalations or reductions will progress with modifications based on the clinical safety, tolerability and preliminary PK data consideration of the area under the concentration-time curve (AUC) from time zero to 24 hours after dosing (AUC[0-24]) and maximum plasma concentration (Cmax) exposures based on the no-observed-adverse-effect-level (NOAEL) from the preceding cohorts.

Holter monitoring will be performed on Day 1 for extraction of ECGs paired with PK sampling. Continuous ECG recording will not be performed during the food effect periods. In case the cardiodynamic evaluation is undertaken at a later time, please refer to Section 8.2.4.2.

In Part 1, participants will remain in the clinical unit from admission on Day-1 until all scheduled safety and pharmacokinetic assessments have been completed for that dose (approximately 5 days) for each period. The duration of study participation will be approximately 3 months (~30 days screening, 5 days in-house assessment for the completion of each of the four periods, 2 weeks between each dose escalation and ~14-day follow-up period) for completion of up to four periods. Part 1 will consist of two cohorts with up to a four-period cross-over. The food effect evaluation will be conducted in last period (Period 4) in only one of the cohorts based on the observed human pharmacokinetics.

Part 2: Repeat Dose Escalation in Healthy Adult Participants

Part 2 consists of a maximum of four ascending repeat-dose cohorts (Cohorts 3 to 6), each with 10 participants who will receive a single oral dose of GSK3882347 or placebo for 7 days. The earliest point at which Part 2 of the study will be initiated is once the single dose safety and preliminary PK data at an exposure that exceeds the daily exposure predicted at steady state for the Part 2 planned starting dose of 50 mg is demonstrated in Part 1. The planned starting dose of GSK3882347 in Part 2 is 50 mg administered as once daily Days 1 to Day 7. The dose is planned to increase in subsequent cohorts to 150, 500 and 900 mg. The starting dose and maximum dose may be changed based on clinical safety, tolerability and PK findings in Part 1 or earlier doses in Part 2 and consideration of the area under the concentration-time curve (AUC) from time zero to 24 hours after dosing (AUC[0-24]) and maximum plasma concentration (Cmax) exposures based on the no-observed-adverse-effect-level (NOAEL).

Participants who meet the criteria for study entry will be assigned to the current dose level and randomized to receive GSK3882347 or placebo in a 4:1 ratio before administration of study intervention on Day 1 in Part 2. As a safety precaution, cohorts will be split into two sub-cohorts to allow sentinel dosing. At each dose level (Cohorts 3-6), the first two participants will receive either GSK3882347 or placebo (one active and one placebo). Dosing of the remaining eight participants (seven active and one placebo) in that cohort will occur at least 120 hours later based on review of the safety data (e.g. vital signs, ECGs, clinical laboratory results and adverse events) by the Principal Investigator and sponsor Medical Monitor from all sub-cohorts of sentinel participants. The 120 hour timeframe was selected on the basis of available preclinical data, as GSK3882347 is anticipated to have reached steady-state by 120 hours, however this duration may be increased or decreased based on emerging PK data.

Doses are planned to escalate in a sequential fashion contingent on the preliminary safety, tolerability and pharmacokinetic data from Part 1 and at least 7 days of repeat dosing in a minimum of five participants who received active treatment in the previous cohort in Part 2. The dosing frequency, duration of dosing, and decision to dose (escalations or reductions) in the next dose level may be changed based on the safety, tolerability or pharmacokinetic findings in Part 1 or earlier doses in Part 2.

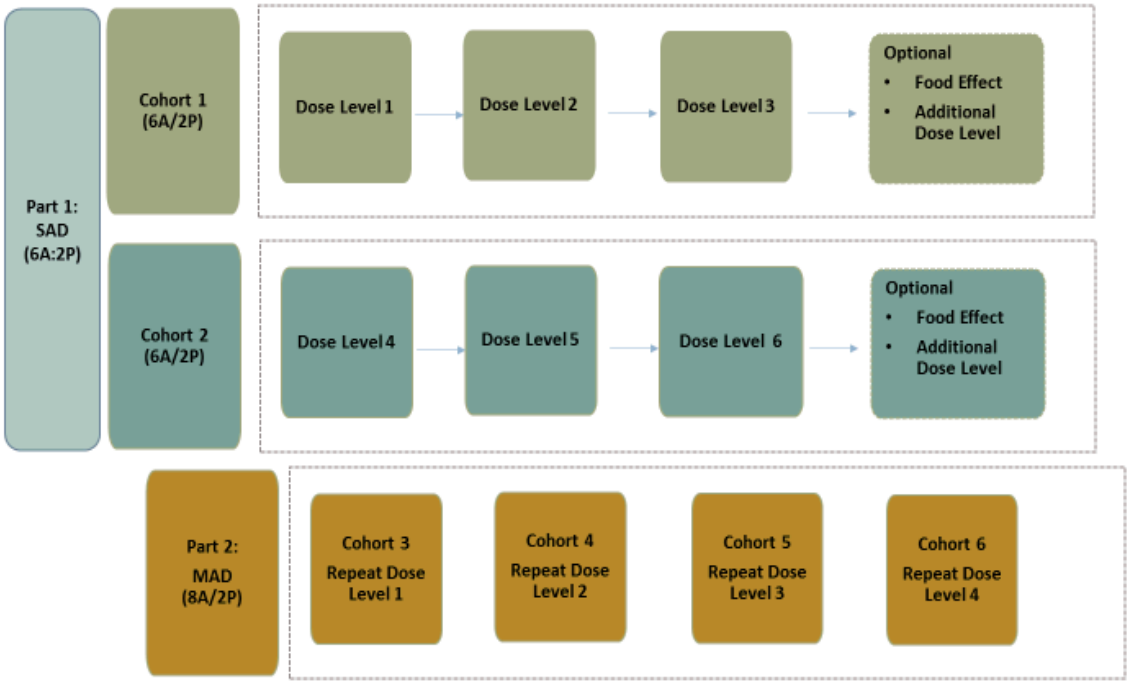
Continuous ECG recording will be performed on Day 1 and Day 7 for extraction of ECGs paired with PK sampling.

In Part 2, participants will remain in the clinical unit from admission on Day-1 until after all scheduled safety and pharmacokinetic assessments have been completed (approximately 5 days post the last dose or 5 half-lives, whichever is longer based on the emerging data from Part 1). The duration of study participation will be up to approximately 8 weeks (~30 days screening, up to 12 days in-house assessment period, and ~14-days follow-up period).

Dose Escalation Committee: Yes

1.2. Schema

Figure 1 Study Design Schema



Notes

- A = active, P = placebo
- SAD = single ascending dose; MAD multiple ascending dose
- Starting SAD dose (Dose Level 1) = (i.e. 50 mg)
- Subsequent dose escalations will be determined based on safety and PK data
- Part 2 (MAD) may start in parallel with Part 1 (SAD)
- Figure shows illustration of planned dosing strategy, which may be changed or cancelled based on preliminary safety, tolerability and PK from preceding doses; and does not represent the randomization strategy

1.3. Schedule of Activities (SoA)

Table 1 Time and Events Table: Screening and Follow-up Visits; Single and Repeat Dose Escalation (Parts 1 and 2)

Procedure	Screening Period (up to 30 days before Day 1)	Follow-up Visit (14 days ± 3 days after the last study intervention)	Notes
Informed consent	X		
Inclusion and exclusion criteria	X		Recheck clinical status before randomization and/or first dose of study intervention
Demography	X		
Medical history (includes substance usage and family history of premature cardiovascular disease) and medication history	X		Substances: drugs, alcohol, tobacco and caffeine
Full physical examination including height and weight	X		
Brief physical examination		X	Additional exams/screens may be performed, or brief exams made full exams by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate)
AE Review		X	
SAE Review	X	X	Serious AEs will be collected from the signing of informed consent
Concomitant medication review	X	X	
Vital signs (BP, HR, tympanic temperature, respiration rate)	X	X	Single measurements will be obtained
Holter monitoring	X		Approximately 24-hour screening
12-lead safety electrocardiogram	X	X	Single measurements will be obtained
Clinical chemistry (including liver chemistries), hematology, and urine tests (including urine creatinine)	X	X	
Human Immunodeficiency Virus (HIV), Hepatitis B surface antigen and hepatitis C screen	X		
COVID-19 screening	X		Frequency in accordance with site procedures
Urine Drug, Smoke Breathalyzer and Alcohol Breath Tests	X		

Procedure	**Screening Period (up to 30 days before Day 1)**	**Follow-up Visit (14 days ± 3 days after the last study intervention)**	**Notes**
b-hCG pregnancy/Estradiol/FSH Tests	X		Pregnancy test as appropriate. Urine Pregnancy Kits (HCP Pregnancy Test Strip). Estradiol and FSH at screening as appropriate. Only women of non-childbearing potential may participate
Stool microbiome collection		X	Participants will be given instructions and collection items for specimen collection for the follow up visit. The stool sample can be collected up to 72 hours (3 days) prior to the visit the stool sample is required (Follow-up). Total of 3 collection time points: Day -1, prior to discharge and follow-up. The other sample collections can be found in SoA Table 2 for Part 1 and Table 3 and Table 4 for Part 2.
Out Patient Visit	X	X*	*At least 7 days and no greater than 14 days after the last study intervention Additional follow-up visits may be scheduled if there are clinical findings at the follow-up visit
AE = adverse event, β-hCG = beta human chorionic gonadotropin, BP = blood pressure, FSH = follicle-stimulating hormone, HR = heart rate, SAE = serious adverse event.			

- The timing and number of planned study assessments, including: safety and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) 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 EC before implementation.

Table 2 Part 1 - Single Dose Escalation and Food Effect

	Study Days																		
Procedure	**-1**	**1**												**2**		**3**	**4**	**5**	**Notes**
		Predose	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**32**	**48**	**72**	**96**	**Hours relative to study intervention**
Inclusion and exclusion criteria	X																		
Brief physical examination	X													X		X		X	
Urine Drug, Smoke Breathalyzer/Alcohol Breath Tests	X																		Additional testing may be performed at other timepoints
β-hCG pregnancy test	X																		Pregnancy test as appropriate
Admission to clinical unit	X																		Participants to be admitted to the unit the day before dosing (Day -1) and remain in house until discharge
Randomization		X																	Randomization will occur before first dose in Period 1
Administration of study intervention			X																No minimum time interval is required between the sentinels at each dose level. Approximately 15 minutes will be observed between the dosing of the remaining participants
AE Review			X	←----------Continuous review----------→															
SAE Review	←----------Continuous review----------→																		Serious AEs will be collected from the signing of informed consent.

	Study Days																		
Procedure	**-1**	**1**												**2**		**3**	**4**	**5**	**Notes**
		Predose	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**32**	**48**	**72**	**96**	**Hours relative to study intervention**
Ad hoc COVID-19 testing based on clinical presentations and site procedures	←----------Continuous review----------→																	X	Sample collected upon discharge
Concomitant medication review			X	←----------Continuous review----------→															
Vital signs (BP, HR, tympanic temperature, respiration rate)	X	X*				X		X	X	X	X	X		X		X	X	X	*Triplicate measurements of blood pressure and pulse rate will be obtained pre-dose and averaged. Single measurements will be obtained at all other timepoints. Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak drug concentrations for subsequent cohorts.
12-lead safety electrocardiogram	X	X*				X		X	X	X	X	X		X					Triplicate 12-lead safety ECGs will be obtained no more than 15 minutes apart within 1-hour pre-dose and single measurements will be obtained at all other timepoints.

	Study Days																		
Procedure	**-1**	**1**												**2**		**3**	**4**	**5**	**Notes**
		Predose	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**32**	**48**	**72**	**96**	**Hours relative to study intervention**
Continuous cardiac monitoring**		X*	←----------Continuous review----------→																**Participants will be semi-supine resting for at least 10 minutes prior to and 5 minutes after each time point for ECG extractions. *3 time points (-45, -30 and -15 minutes) prior to dosing. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should occur in that order. Will not be collected in food effect.
Clinical chemistry (including liver chemistries), hematology, and urine tests (including urine creatinine)	X													X		X	X	X	
PK Blood Sample		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Details of PK sample collection and storage will be provided in the Study Reference Manual.
Metabolite Blood Sample		X		X	X	X	X	X	X	X	X	X	X	X					No metabolite blood samples will be collected in the food effect groups

	Study Days																		
Procedure	**-1**	**1**												**2**		**3**	**4**	**5**	**Notes**
		Predose	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**32**	**48**	**72**	**96**	**Hours relative to study intervention**
PK/Metabolite Urine Sample		X	See urine collection sampling times*																*Urine collection times (hours) 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-22, 22-24, 24-26, 26-32, 32-38, 38-48, 48- 60, 60-72, 72-84, 84-96 post dosing. If participant is unable to void at a specified timepoint, this should be recorded in the CRF. Participants will void bladder prior to dosing. Voids from urine will be combined into 0-24 hr pool for metabolite analysis, after aliquots for PK are removed.
Genetic sample (optional)		X																	Collect the genetic sample only if the participant has a signed consent specific for this purpose. Informed consent for optional sub-studies (e.g., genetics research) must be obtained before collecting a sample.

	Study Days																		
Procedure	**-1**	**1**												**2**		**3**	**4**	**5**	**Notes**
		Predose	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**32**	**48**	**72**	**96**	**Hours relative to study intervention**
Stool microbiome collection/ stool type assessment*	X	*Continuous stool type assessment of all bowel movements while in the clinical unit.																X	Participants will be given instructions and collection items for specimen collection. The stool sample can be collected up to 72 hours (3 days) prior to the visit the stool sample is required (Day -1 and Day 5). A last sample will be collected on the day closest to the day of discharge (Day 5). The follow-up sample is indicated in SoA Table 1.

	Study Days																		
Procedure	**-1**	**1**												**2**		**3**	**4**	**5**	**Notes**
		Predose	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**32**	**48**	**72**	**96**	**Hours relative to study intervention**
Meal (post dose)	X	See Notes for meal times																	Prior to dosing, participants will fast for 8 hrs overnight. No food is allowed for at least 4 hrs post-dose; after which meals will be permitted as per site schedule. Participants will receive standardized meals scheduled at the same time in each period. Water is permitted with dosing and at all times except 1-hour pre-dose through 2-hours post-dose.
Test Meal		X																	Food Effect (Period 4) Part 1 only, participants will eat a high fat meal prior to dosing as specified in the Study Reference Manual.
Daily fluids (intake/output)		X*	See assessment times											X		X	X	X	*Assessed approximately over 24 hours
Discharge																		X	
AE = adverse event, BP = blood pressure, HR = heart rate, PK = Pharmacokinetic, SAE = serious adverse event.																			

- The timing and number of planned study assessments, including: safety and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) 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 EC before implementation.

Table 3 Part 2 – 7-Day Repeat Dose Escalation (Days 1 and 7)

	Study Days													
Procedure	**1 and 7**													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
Inclusion and exclusion criteria	X													Recheck clinical status before randomization and/or 1st dose of study treatment
Brief physical examination	X													
Urine Drug, Smoke Breathalyzer/Alcohol Breath Tests	X													Additional testing may be performed at other timepoints
β-hCG pregnancy test	X													Pregnancy test as appropriate
Admission to clinical unit	X													
Randomization		X												Randomization will occur before first dose on Day 1 only.
Administration of study intervention			X											
AE Review			X	←----------Continuous review----------→										
SAE Review	←----------Continuous review----------→													Serious AEs will be collected from the signing of informed consent.
Ad hoc COVID-19 testing based on clinical presentation and site procedures	←----------Continuous review----------→													
Concomitant medication review			X	←----------Continuous review----------→										

	Study Days													
Procedure	**1 and 7**													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
Vital signs (BP, HR, tympanic temperature, respiration rate)	X	X*				X		X	X	X	X	X		Vital signs will be obtained within 1 hour of pre-dose and at 1, 2, 4, 6, 8, 12 and 24 hours after study administration on Days 1 and 7. *Triplicate readings of blood pressure and pulse rate will be taken pre-dose and averaged on Days 1 and 7. Single measurements will be obtained at all other timepoints. Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.

	Study Days													
Procedure	**1 and 7**													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
12-lead safety electrocardiogram	X	X*				X		X	X	X	X	X		*Triplicate 12-lead safety ECGs will be obtained no more than 15 minutes apart within 1-hour pre-dose on Days 1 and 7. Single 12-lead safety ECGs will be obtained at 1, 2, 4, 6, 8, 12 and 24 hours after study administration on Days 1 and 7.
Continuous cardiac monitoring**		X*	←----------Continuous review----------→											**Participants will be semi-supine resting for at least 10 minutes prior to and 5 minutes after each time point for ECG extractions. *3 time points (-45, -30 and -15 minutes) prior to dosing on Day 1. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should occur in that order.

	Study Days													
Procedure	**1 and 7**													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
Clinical chemistry (including liver chemistries), hematology, and urine tests (including urine creatinine)	X													
PK Blood Sample		X		X	X	X	X	X	X	X	X	X	X	Details of PK sample collection and storage will be provided in the Study Reference Manual.
4β-hydroxycholesterol sampling		X												Sample to be taken pre-dose on Day 1 in a fasted state.
Metabolite Blood Sample		X		X	X	X	X	X	X	X	X	X	X	
PK/Metabolite Urine Sample		X	See urine collection times*											*Urine collection times (hours) 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-22, 22-24 post dosing. Participants will void bladder prior to dosing. 0-24-hr urine samples will be collected. Voids from urine will be combined into 0-24 hr pool for metabolite analysis, after aliquots for PK are removed.

	Study Days													
Procedure	**1 and 7**													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
Genetic sample (optional)		X												Collect the genetic sample only if the participant has a signed consent specific for this purpose. Informed consent for optional sub-studies (e.g., genetics research) must be obtained before collecting a sample.
Stool microbiome collection/ stool type assessment*	X	*Continuous stool type assessment of all bowel movements while in the clinical unit.												Participants will be given instructions and collection items for specimen collection. The stool sample can be collected up to 72 hours (3 days) prior to the visit the stool sample is required (Day -1).

	Study Days													
Procedure	1 and 7													**Notes**
	-1	**Predose**	**0**	**0.25**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**16**	**Hours relative to study intervention**
Meal (post-dose)	X	See Notes for meal times												Prior to dosing on Days 1 and 7, participants will fast for 8 hrs overnight. No food is allowed for at least 4 hrs post-dose; after which meals will be permitted as per site schedule. Water is permitted with dosing and at all times except 1-hour pre-dose through 2-hours post-dose. Participants will receive standardized meals scheduled at the same time in each period.
Daily fluids (intake/output)		X*	See assessment times.											*Assessed approximately over 24 hours

AE = adverse event, BP = blood pressure, HR = heart rate, PK = Pharmacokinetic, SAE = serious adverse event.
24-hour procedures are presented in Table 4.
The 4β-hydroxycholesterol sample may not be available from all Cohorts in Part 2, due to the timing of the amendment when this was added.

- The timing and number of planned study assessments, including: safety and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) 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 EC before implementation.

Table 4 Part 2 – 7-Day Repeat Dose Escalation (Days 2 through 6 and Day 8 to 12)

	Study Days									
Procedure	**2**		**3**	**4**	**5**	**6**	**8**		**9-12**	**Notes**
	(24hrs post-Day 1 dose)	**0**	**0**	**0**	**0**	**0**	**(24 hrs post-Day 7 dose)**	**0**	**0**	
Brief physical examination		X	X	X	X	X		X	X*	*Upon discharge
Administration of study intervention		X	X	X	X	X				No minimum time interval is required between the sentinels at each dose level. Approximately 15 minutes will be observed between the dosing of the remaining participants
AE Review	←----------Continuous review----------→									
SAE Review	←----------Continuous review----------→									
Ad hoc COVID-19 testing based on clinical presentation and site procedures	←----------Continuous review----------→								X*	*Sample collected just prior to discharge for COVID-19 testing
Concomitant medication review	←----------Continuous review----------→									

	Study Days									
Procedure	**2**		**3**	**4**	**5**	**6**	**8**		**9-12**	**Notes**
	(24hrs post-Day 1 dose)	**0**	**0**	**0**	**0**	**0**	**(24 hrs post-Day 7 dose)**	**0**	**0**	
Vital signs (BP, HR, tympanic temperature, respiration rate)	X		X	X	X	X	X		X	Single measurements will be obtained within 1-hour pre-dose and daily in the morning on days 9-12 until discharge. Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.
12-lead safety electrocardiogram	X		X	X	X	X	X		X	Single 12-lead safety ECGs will be obtained within 1 hour before pre-dose and daily in the morning on days 9-12 until discharge.

	Study Days									
Procedure	**2**		**3**	**4**	**5**	**6**	**8**		**9-12**	**Notes**
	(24hrs post-Day 1 dose)	**0**	**0**	**0**	**0**	**0**	**(24 hrs post-Day 7 dose)**	**0**	**0**	
Continuous cardiac monitoring**	X						X			**Participants will be semi-supine resting for at least 10 minutes prior to and 5 minutes after each time point for ECG extractions. When ECG extractions coincide with safety ECGs, vital signs assessment and blood draws, procedures should occur in that order.
Clinical chemistry (including liver and kidney chemistries), hematology, and urine tests (including urine creatinine)		X	X	X	X	X		X	X*	*Just prior to discharge.
PK Blood Sample	X		X*	X*	X*	X*	X			*Trough PK samples
4β-hydroxycholesterol sampling							X			Sample to be taken at 24hr post AM dose on Day 7. Sample should be in a fasted state.
PK Metabolite Sample	X						X			
PK Urine Sample	X		X*	X*	X*	X*	X			*Trough PK samples

	Study Days									
Procedure	**2**		**3**	**4**	**5**	**6**	**8**		**9-12**	**Notes**
	(24hrs post-Day 1 dose)	**0**	**0**	**0**	**0**	**0**	**(24 hrs post-Day 7 dose)**	**0**	**0**	
Stool microbiome collection/ stool type assessment*	*Continuous stool type assessment of all bowel movements while in the clinical unit.								X**	A last sample will be collected on the day closest to the day of discharge. The stool sample can be collected up to 72 hours (3 days) prior to the visit the stool sample is required (Days 9-12). **This includes the last sample collected on the day closest to the day of discharge (Days 9-12) for microbiome. The Day -1 sample is indicated in SoA Table 4 and follow-up sample is indicated in SoA Table 1.
Meal		X	X	X	X	X		X	X	Participants will receive standardized meals scheduled at the same time in each period.
Daily fluids (intake/output)	X						X			

	Study Days									
Procedure	**2**		**3**	**4**	**5**	**6**	**8**		**9-12**	**Notes**
	(24hrs post-Day 1 dose)	**0**	**0**	**0**	**0**	**0**	**(24 hrs post-Day 7 dose)**	**0**	**0**	
Discharge								X	X	Participants will be discharged from the clinical unit after the assessments are completed.

AE = adverse event, BP = blood pressure, HR = heart rate, PK = Pharmacokinetic, SAE = serious adverse event.
The 4β-hydroxycholesterol sample may not be available from all Cohorts in Part 2, due to the timing of the amendment when this was added.

- The start of Part 2 can be modified from emerging data from Part 1.
- The timing and number of planned study assessments, including: safety and pharmacokinetic assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) 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 EC before implementation.

2. INTRODUCTION

GSK3882347, a FimH (bacterial adhesin) antagonist, is a potent, novel non-antibiotic that is being developed for the treatment of uncomplicated urinary tract infections caused by uropathogenic Escherichia coli (UPEC).

2.1. Study Rationale

The goal of this study is to evaluate the safety, tolerability and pharmacokinetic properties (including food effect) of GSK3882347 to enable clinical development of the molecule as an antibiotic-sparing treatment for uncomplicated urinary tract infections.

Bacteria possess adhesins, which are cell-surface components or appendages that facilitate adhesion or adherence to other cells or to surfaces. GSK3882347 is a potent and specific competitive antagonist of the Escherichia coli type 1 pilus adhesin molecule FimH, designed to disrupt the interaction between FimH and mammalian mannose-rich glycoproteins, such as uroplakin Ia and integrins in the bladder epithelium and other epithelia.

GSK3882347 is being developed as an antibiotic-sparing medicine to treat or prevent infection of the bladder mucosa, via inhibition of FimH protein function on UPEC, which cause approximately 85% of all urinary tract infections. It is anticipated that the use of GSK3882347 will help combat the increasing antimicrobial resistance (AMR) to traditional antibiotics that threatens to increase greatly the economic burden, morbidity and mortality associated with bacterial infections [O'Neill, 2016].

Preclinical data in a murine urinary tract infection (UTI) model supports the use of a FimH antagonist in both the treatment and prevention of uncomplicated UTI (uUTI) in both infection naïve mice and previously infected mice (a recurrent UTI (rUTI) model). *In vitro* data indicate that GSK3882347 is an effective antagonist of FimH in a broad range of clinical UPEC strains. Further, GSK3882347 was effective against a subset of these strains representing all the major UPEC FimH alleles in both the murine UTI treatment model and in an *in situ* human bladder tissue binding assay. GSK3882347 inhibited binding in a concentration-dependent manner by >95% at 30 µM (or less). *In vivo* efficacy studies were also completed using the acute therapeutic model in mice with UPEC strain UTI89 to correlate microbiological efficacy and urinary exposure. A preliminary PK/PD target for GSK3882347 was determined as the maintenance of a trough concentration of ≥5 µM in urine for the duration of the dosing period. Based on the studies described above, a target Cmin concentration range of 5-30 µM was defined to support dose selection in this study.

2.2. Background

UTIs are very common, with approximately 11% of women >18 years of age experiencing at least 1 episode of acute cystitis per year [Foxman, 2000]. Of these, half will experience more than 1 recurrent episode over their lifetime [Foxman, 2000]. The peak incidence of acute cystitis occurs in young, sexually active women ages 18 to 29 years [Fihn, 2003]. The predominant uropathogen isolated in community-acquired

UTIs is *E. coli* (75% to 90%) followed by *S.saprophyticus* (5% to 15%) [Stamm, 1993; Talan, 2000; Foxman, 2010]. *Klebsiella*, *Enterobacter*, and *Proteus* species and enterococci are observed in only 5% to 10% of cases [Stamm, 1993; Talan, 2000; Foxman, 2010].

Multidrug resistance, which is typically associated with nosocomial infections, has now emerged at the community level and has made treatment approaches for UTIs more difficult [Hooton, 2012; Flamm, 2014; Sanchez, 2016]. This has led to increasing patient morbidity, increasing costs due to reassessment and retreatment, higher rates of hospitalization, and increased use of broad-spectrum antibiotics [Foxman, 2002; Gupta, 2011a; Hooton, 2012].

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

Continuous low dose antibiotic is effectively prophylaxis for recurrent urinary tract infections (rUTI). Other options include postcoital antibiotic prophylaxis prevention in sexually active females, vaginal estrogen in postmenopausal women, other treatments and behavioural modifications. With the rise of antibiotic resistance, additional treatment strategies and prevention measures for rUTI has led to potential non-antibiotic treatment approaches for rUTI.

GSK3882347 will be the first antibiotic-sparing medicine to treat or prevent infection of the bladder mucosa, via inhibition of FimH protein function on uropathogenic *E. coli* (UPEC), which cause approximately 85% of all UTIs. Use of GSK3882347 will help combat the increasing antimicrobial resistance (AMR) to traditional antibiotics that threatens to increase greatly the economic burden, morbidity and mortality associated with bacterial infections [O'Neill, 2016].

Summaries of the non-clinical safety and pharmacology are included in the GSK3882347-Investigator's Brochure [GlaxoSmithKline Document Number 2019N403317_01, 2020].

In light of the global COVID-19 pandemic, all participants will be screened for COVID-19 prior to, during and at the end of the study period. Please see further details for risk assessment and mitigation strategy below.

2.3. Benefit/Risk Assessment

2.3.1. Acute Monitoring in FTIH Studies

Consistent with GSK standards for early phase studies, the study will be conducted in a Phase 1 Clinical Research Unit with previous experience with first-time-in-human trials and immediate access to hospital facilities for the treatment of medical emergencies.

GSK3882347 will be administered in an in-patient setting (with sufficient overnight facilities) with appropriate monitoring. To minimize the risk of the initial human administration of GSK3882347, a sentinel dosing strategy will be utilized at each dose level: 1 participant will receive GSK3882347 and 1 participant will receive placebo. After the GSK Medical Monitor and Principal Investigator have reviewed the safety data through 24 hours post-dose in the Part 1 and at least 120 hours in Part 2, the remaining participants from that cohort will be dosed.

Once all assessments through 24 hours post-dose have been completed in a minimum of four participants on active treatment in Part 1 and at least 7 days of dosing in a minimum of 5 participants on active treatment in Part 2, the GSK team and the investigator will review all the available safety and PK data from all participants before proceeding to the next dose level. Additional information can be found in the Dose Escalation Plan. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3882347 may be found in the GSK3882347 Investigator's Brochure [GlaxoSmithKline Document Number 2019N403317_01, 2020]. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.2. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK 3882347		
Gastrointestinal toxicity **(including body weight loss, decreased food consumption and dehydration)**	Dogs given ≥300 mg/kg/day had severe body weight loss, decreased food consumption, dehydration, emesis and abnormal feces. Dogs given 1000 mg/kg/day were euthanized early due to severity of body weight loss. Pregnant rabbits given ≥300 mg/kg/day had severe body weight loss and decreased food consumption, which resulted in early euthanasia and 1 early death at 900 mg/kg/day. These changes in dogs and rabbits resulted in early euthanasia or death at the doses stated. Nonclinical Risks – concluding sections of the Non-Clinical Assessment of Safety (NCAS) should provide key nonclinical risks associated with the IP.	• Dosing for a maximum of 7 days. • Standard clinical monitoring with elicitation of clinical symptoms; physical examinations and routine safety blood haematology and chemistry tests. • Monitoring for AEs. • Monitoring daily fluid balance in participants. • Gastrointestinal stopping criteria: Participant will continue to dose through grade 1 toxicity, interrupt dosing for grade 2 toxicity and discontinue drug for grade 3-4 toxicity (for the latter, consultation with GI experts will occur with no plan for drug restart) (see Section 7.1.1) • Monitoring of stool type with the Bristol stool chart to identify changes in bowel

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		habit which may represent gastrointestinal toxicity.
OTHER		
COVID-19	Participation within a hospital environment may increase risk of contracting COVID-19. Exposure to other participants and staff may increase risk of exposure.	• Monitoring of clinical presentation of COVID-19 signs/symptoms. • Conduct study at sites which have appropriate mitigation strategies in place.

2.3.3. Benefit Assessment

This is a study in healthy participants; no medical benefit will be derived by volunteers' participation. However, participants in this study may be contributing to the development of new therapies in an area of unmet need.

2.3.4. Overall Benefit: Risk Conclusion

Given the preclinical profile of GSK3882347, measures taken (careful selection of the participants and the extent of safety monitoring incorporated into the study) and the planned clinical procedures and evaluations in this study, the potential risks to participants receiving GSK3882347 are low, evaluable, and manageable.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3882347 following oral administration of single and repeat doses in healthy adult participants	• Occurrence of adverse events (AEs) and treatment related AEs • Occurrence of clinically significant changes in vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings
• To evaluate the pharmacokinetics of GSK3882347 in plasma and urine following oral administration of single and repeat doses in healthy adult participants	• Single dose (plasma): AUC(0-24), AUC(0-t), AUC(0-inf), Cmax, C24h, tmax, tlag and t1/2 of GSK3882347, as data permit • Repeat dose (plasma): AUC(0-tau), Cmax, tmax and Ctau of GSK3882347, as data permit • Urine concentration at 22-24h collection time-point • Amount excreted in urine (Ae) of unchanged GSK3882347, fraction of the dose excreted in urine (fe) and renal clearance (CLr), as data permit
Secondary	
• To further evaluate the pharmacokinetics of GSK3882347 in plasma	• Single dose(plasma): AUC(0-12), C12h,CL/F, Vd/F and MRT of GSK3882347, as data permit

Objectives	Endpoints
• To examine dose proportionality of GSK3882347 following oral administration of single and repeat doses in healthy adult participants • To evaluate the extent of accumulation, time invariance, and achievement of steady-state of GSK3882347 following oral administration of single and repeat doses in healthy adult participants	• Repeat dose (plasma): AUC(0-12) and C12h of GSK3882347, as data permit • AUC(0-inf) and Cmax for single dose and AUC(0-tau) and Cmax for repeat dose, as data permit • Ro (accumulation ratio) using AUC(0-tau) for repeat dose, as data permit • Time invariance using AUC(0-tau) (repeat dose) and AUC(0-inf) (single dose) • Achievement of steady-state (Ctau collected on multiple days)
• To evaluate the effect of food on pharmacokinetics of GSK3882347 following oral administration of single dose in healthy adult participants	• AUC(0-24), AUC(0-t), AUC(0-inf), C24h, Cmax, tmax and tlag, as data permit
Exploratory	
• To assess ECG effects of GSK3882347, including concentration-QTc analysis, following single and repeat doses in healthy adult participants	• Change-from-baseline QTc (ΔQTcF) • Change-from-baseline heart rate, PR and QRS interval (ΔHR, ΔPR and ΔQRS) • Placebo-corrected ΔQTcF, ΔHR, ΔPR and ΔQRS • Treatment emergent T-wave abnormalities and presence of U-waves • Categorical outlier analysis for HR, QTcF, PR and QRS

Objectives	Endpoints
• To investigate the plasma and urine metabolic pathways of GSK3882347 in healthy participants	• Characterization of the plasma and urinary metabolites of GSK3882347, estimation of the percentage dose eliminated in urine, where possible
• To characterize the effect of GSK3882347 on intestinal microbiota following single and repeat doses in healthy adult participants	• Change in intestinal microbiome over time
• To assess potential effect of repeat doses of GSK3882347 on Cytochrome P450 3A4 (CYP3A4) enzyme activity in Part 2	• Plasma 4β-hydroxycholesterol to cholesterol ratio at pre-treatment and following repeat dosing of GSK3882347

Note: The exploratory endpoints may be analyzed as GSK3882347 clinical development continues.

4. STUDY DESIGN

4.1. Overall Design

This is a two-part phase I, FTIH, randomized, double-blind, single-center, placebo-controlled, dose-escalation study to determine the safety, tolerability and pharmacokinetics of GSK3882347 following oral administration of single (Part 1) and repeat doses (Part 2) in healthy adult men and WONCBP. Part 1 will consist of two cohorts with a maximum of four-period cross-over. The food effect evaluation will be conducted in the last period (Period 4) in only one of the cohorts based on the observed human pharmacokinetics.

During Parts 1 and 2, participants who meet the criteria for study entry will be assigned to the current dose level and randomized to receive GSK3882347 or placebo before administration of study intervention on Day 1.

Dose escalation will be conducted only if it is supported by safety, tolerability and pharmacokinetic results from the preceding dose level(s). This is the first administration of GSK3882347 in humans; therefore, preliminary safety, tolerability and pharmacokinetic results will be reviewed internally at GSK in conjunction with the study site and study design adjustments may be made based on emerging data from each dose cohort. The repeat dose escalation component (Part 2) of this study will be initiated once safety at an exposure that exceeds the daily exposure predicted at steady state for the Part 2 planned starting dose of 50 mg has been demonstrated in Part 1. This is predicted to occur at the 250 mg single dose. The point at which Part 2 is initiated can be modified based on the emerging safety, tolerability and pharmacokinetic data from Part 1.

In Part 1, participants will remain in the clinical unit from admission on Day-1 until all scheduled safety and pharmacokinetic assessments have been completed for that dose (approximately 5 days) for each period. The duration of study participation will be approximately 3 months (~30 days screening, 5 days in-house assessment for the

completion of a maximum of the four periods, 2 weeks between each dose escalation and ~14-day follow-up period) for completion of up to four periods. Part 1 will consist of two cohorts with up to a four-period cross-over. The food effect evaluation will be conducted in last period (Period 4) in only one of the cohorts based on the observed human pharmacokinetics.

In Part 2, participants will remain in the clinical unit from admission on Day-1 until after all scheduled safety and pharmacokinetic assessments have been completed (approximately 5 days post the last dose or 5 half-lives, whichever is longer based on the emerging data from Part 1). The duration of study participation will be up to approximately 8 weeks (~30 days screening, up to 12 days in-house assessment period, and ~14-days follow-up period).

Study schematic is provided in Figure 1.

4.2. Scientific Rationale for Study Design

The current study has been designed to address regulatory guidance for FTIH studies in particular General Considerations for Clinical Trials [The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E8/ Committee For Proprietary Medicinal Products (CPMP)/ICH/291/95] and Guideline on Strategies to Identify and Mitigate Risk for First time in -Human Clinical Trials with Investigational Medical Products [EMEA/CHMP/SWP/28367/07] including participant selection, estimation of starting dose, precautions that are applied within and between dosing cohorts, dose escalation scheme, risk mitigation, and stopping rules.

This study represents the first administration of GSK3882347 in humans. The aim of the FTIH is to generate human safety, tolerability and pharmacokinetics of GSK3882347 in healthy participants. The study will be conducted in healthy adult participants comprising of healthy adult men and WONCBP.

Scheduled assessments of subjective symptoms, and objective clinical laboratory tests, vital signs, and 12-lead safety electrocardiograms (ECGs) will be obtained to monitor participant safety.

The single dose assessments in Part 1 will be conducted to determine safety, tolerability and pharmacokinetics of the study intervention in individuals before progressing to doses explored further in other parts of the study and will allow for any adjustments needed based on emerging safety, tolerability and PK data. Part 1 will also include the evaluation of the effect of food on GSK3882347.

Part 2 of this study is planned to include 7 days of repeat dosing to provide sufficient safety, tolerability, and PK as this is the anticipated dosing duration which will be used in females with recurrent UTI (rUTI). The dosing duration may be adjusted depending on PK data collected in Part 1 of the study.

Preclinical studies following oral administration as a suspension to rat and mini-pig, demonstrated that bioavailability was moderate (~40%) suggesting incomplete absorption of compound from the GI tract since first pass hepatic extraction was predicted to be low.

Bioavailability in the female rat following IP administration, which bypasses the GI tract, but not the liver, was ~75%, further supporting this supposition. The solubility in FeSSIF (Fed-state simulated intestinal fluid, pH 6.5) was significantly higher than solubility observed in SGF (simulated gastric fluid) and FaSSIF (Fasted-state simulated intestinal fluid). The concentration in FaSSIF is 0.4 to 0.5 mg/mL. The FeSSIF solubility was higher than the experimental maximum (1.13 mg/mL); therefore, the maximum solubility achievable in GI fluids is not yet known.

Following review of safety, tolerability, and pharmacokinetic data in Part 1, the food effect dose of GSK3882347 will be selected based on an assessment of the ongoing data from the prior single ascending doses. The formulation used for this study will be a capsule of GSK3882347 prepared by extemporaneous compounding. The preliminary results will be used to determine whether an effect of food on GSK3882347 can be anticipated in future studies which will utilise a tablet formulation and will help to guide the pivotal food effect study and commercialization [DHHS, 2019].

Current preclinical data and dose predictions do not indicate any cardiovascular risk. The study will evaluate the exposure-response relationship between GSK3882347 and QTcF as a possible alternative to conducting a thorough QT/QTC study [Darpo, 2014]. ECG wave forms will be collected in both parts and stored for potential analysis, depending on observed PK and other project considerations. The food effect in Part 1 will not be part of the cardio-dynamic evaluation.

A definitive *in vitro* study using human hepatocytes revealed that GSK3882347 was moderate inducer of CYP3A4. Based on the *in vitro* data and using preliminary risk assessments, GSK3882347A has the potential to perpetrate DDIs when co-dosed with CYP3A4 substrates, including oral contraceptives (OCs), resulting in a potential loss of efficacy of OCs and other substrates. Therefore, plasma 4β-hydroxycholesterol, a potential *in vivo* marker of CYP3A4 enzyme activity will be measured within Part 2 (subset - not all cohorts). A comparison will be made between the ratio of 4β-hydroxycholesterol: cholesterol in plasma at baseline and on Day 8 (i.e. approximately 24 hours after the Day 7 dose) in order to assess potential changes in CYP3A4 enzyme activity following repeat dosing of GSK3882347. This information, combined with PBPK modelling, may help to better inform the risk of co-administering GSK3882347 with OCs in future clinical studies which may include women of childbearing potential.

4.3. Justification for Dose

Estimated human pharmacokinetics for GSK3882347 were generated using a physiologically based pharmacokinetic (PBPK) model that correlates plasma and urine exposures incorporating estimates of renal and non-renal clearance derived from single species scaling of observed *in vivo* male rat and dog data. The predicted human clearance of GSK3882347 using rat or dog data differed by approximately 10-fold, therefore, two separate predictions of likely human pharmacokinetics and exposure for GSK3882347 in plasma and urine were established for a 70 kg human.

The highest planned dose in this study is 900 mg, which, for the human exposure prediction based on dog PK, provides 1.8-fold coverage to the rat NOAEL, when dosed

once-daily repeat doses. The doses in the protocol may be amended based on emerging human safety and PK data, however the human exposure will remain below the rat NOAEL and ICHQ3 principles will be followed to ensure that any impurities present in the drug product remain at acceptable levels if dose levels above 900 mg are used.

4.3.1. Starting dose

A single dose of 50 mg of GSK3882347 has been selected as the first dose to be administered to humans. This starting dose is calculated to have a 48.3-fold NOAEL safety margin to the human AUC_{0-24} predicted based on the dog PK and a 251-fold safety margin to the human AUC_{0-24} predicted based on the rat PK (Table 5 and Table 6). An 81.0-fold NOAEL safety margin to the human Cmax is predicted based on the dog PK and a 205-fold safety margin is predicted using the rat PK (Table 5 and Table 6).

Margins to the rat GLP toxicity study NOAEL are presented as the systemic exposure was lower in the rat as compared to the dog at the NOAEL (most conservative approach). The NOAEL in the 14-day GLP rat toxicity study was the top dose of 450 mg/kg/day and was associated with an $AUC_{0-24,SS}$ of 193 µg*h/mL and Cmax of 16.2 µg/mL. As GSK3882347 does not have a human target, the Minimal Anticipated Biological Effect Level (MABEL) in humans for GSK3882347 could not be calculated.

The planned doses for dose escalation in Part 1 after dosing the first cohort with 50 mg are 150, 250, 500, 750, and 900 mg. Following each dose, the systemic PK (up to 24h post-dose) and safety data will be evaluated. The systemic exposure, Cmax and AUC (up to 24h) (where data permits) will be calculated for the current dose and predicted for the next dose level assuming linear PK. The predicted Cmax and AUC will be compared with the NOAEL from the rat and dog preclinical toxicology studies. The proposed dose for the next cohort may be modified if necessary; increments will be no greater than 3.5-fold.

Table 5 Predicted Human AUC0-24 and Cmax Safety Margins Following Single and Multiple Dose Administration of GSK3882347 (Predicted Human PK Based on Dog PK)

Dose (mg)[§]	Predicted human AUC_{0-24} (µg*h/mL)[#]	Safety fold cover for AUC*	Predicted human Cmax (µg/mL)	Safety fold cover for Cmax*
SAD				
900	40.5	4.77	1.94	8.34
750	38.0	5.08	1.80	9.00
500	32.0	6.03	1.60	10.1
250	19.0	10.2	0.96	16.9
150	11.8	16.4	0.60	27.0
50	4.00	48.3	0.20	81.0
MAD				
900 QD	107	1.80	4.97	3.26
500 QD	80.0	2.41	3.70	4.38
150 QD	26.5	7.29	1.28	12.7
50 QD	8.87	21.8	0.43	37.7

[§] Predicted efficacious exposure 50 mg (based on 5 µM target) and 300 mg (based on 30 µM target).

[#] Predicted AUC_{0-24} at steady-state (SS) was used for the calculations of the MAD safety margins.

* Safety margins calculated using the NOAEL determined based on the 14-day GLP rat toxicity studies as $AUC_{0-24,SS}$ of 193 µg*h/mL and Cmax of 16 µg/mL at the dose of 450 mg/kg/day.

Table 6 Predicted Human AUC and Cmax Safety Margins Following Single and Multiple Dose Administration of GSK3882347 (Predicted Human PK Based on Rat PK)

Dose (mg) §	Predicted human AUC0-24 (µg*h/mL) #	Safety fold cover for AUC*	Predicted human Cmax (µg/mL)	Safety fold cover for Cmax*
SAD				
900	8.61	22.4	0.73	22.3
750	8.12	23.8	0.68	23.8
500	6.64	29.1	0.57	28.3
250	3.76	51.3	0.36	45.1
150	2.29	84.3	0.23	70.1
50	0.77	251	0.08	205
MAD				
900 QD	9.48	20.4	0.81	19.9
500 QD	6.87	28.1	0.60	27.2
150 QD	2.32	83.2	0.23	69.2
50 QD	0.78	248	0.08	203

§ Predicted efficacious exposure 300 mg (based on 5 µM target) and 650 mg (based on 30 µM target).
# Predicted AUC_{0-24} at steady-state (SS) was used for the calculations of the MAD safety margins.
* Safety margins calculated using the NOAEL determined based on the 14-day GLP rat toxicity studies as $AUC_{0-24,SS}$ of 193 µg*h/mL and Cmax of 16.2 µg/mL at the dose of 450 mg/kg/day.

The United States Food and Drug Administration (FDA) guidance suggests calculating a human equivalent dose (HED), based on the NOAEL in the most sensitive or most relevant preclinical species, utilizing scaling factors that are based on differences in body surface area between species. The HED is converted to a maximum recommended starting dose (MRSD) in humans by dividing by a safety factor (default = 10). The safety factor may be adjusted depending on the pharmacology, toxicology, preclinical pharmacokinetics of the drug, or previous experience with compounds in the same pharmacologic/structural class. Using the rat NOAEL, the HED was calculated to be 73 mg/kg. With a safety factor of 10, the estimated MRSD in humans would be 438 mg for a 60 kg human. The MRSD dose is ~ 8.8-fold higher than our proposed initial dose of 50 mg [DHHS, 2005].

4.3.2. Predicted Efficacious Dose

An *in-situ* binding assay was used to characterize GSK3882347 mediated inhibition of UPEC binding to healthy or inflamed human bladder epithelium. Although there was much variation in the level of binding by the strains to human bladder tissue- either healthy or inflamed, all strains tested could be inhibited by GSK3882347 and in the clear majority of cases tissue binding was inhibited by >95% at 30 µM (or less), relative to vehicle controls. *In vivo* efficacy studies were also completed using the acute therapeutic model in mice with UPEC strain UTI89 to correlate microbiological efficacy and urinary exposure. A preliminary PK/PD target for GSK3882347 was determined as the maintenance of a trough concentration of ≥5 µM in urine for the duration of the dosing period. Importantly, achieving this target provided maximal efficacy regardless of dosing

regimen (regimens evaluated: QD, BID, and TID). Based on the studies described above, a target Cmin concentration range of 5-30 µM was defined to support dose selection in this study.

The predicted efficacious doses for humans were calculated using the PBPK model based on the target urine Cmin range of 5-30 µM at day 1 and considering the difference in the rat and dog pharmacokinetics (see Table 7).

Table 7 Anticipated Therapeutic Dose Range Considering Different Target Urine Cmin and Human Predicted Pharmacokinetics Based on Rat and Dog Pre-clinical Data

	Predicted Human Therapeutic Dose	
Urine target Cmin (µM)	**Based on Dog PK**	**Based on Rat PK**
5	50 mg	300 mg
30	300 mg	650 mg

4.3.3. Food Effect

The dose of GSK3882347 to be administered will be determined from Part 1 to ensure an adequate safety margin assuming an arbitrary two-fold increase in exposure to GSK3882347 when administered with food.

4.3.4. Part 2: Starting Dose and Dose Escalation

Four dose levels are planned, with escalation increments no greater than 3.5-fold. The lowest dose is expected to be 50 mg. The highest dose will not exceed the top dose tested in Part 1. Doses and dosing regimen will be based on findings from Part 1 and emerging observations in Part 2.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring. A participant with a clinical abnormality or laboratory parameter(s) not specifically listed in the exclusion or exclusion criteria that is outside the reference range for the population being studied may be included only if the investigator, in consultation with the Medical Monitor (if required), agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

Weight

3. Body weight at least 50.0 kg (110 lbs.) for males and 45.0 kg (99 lbs.) for females; and body mass index (BMI) within the range 18.5 – 32.0 kg/m2 (inclusive).

Sex

4. Male and female participants

a. Female Participants:

A female participant is eligible to participate if she is of non-childbearing potential as defined in Appendix 4

b. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period for at least five days, corresponding to time needed to eliminate study intervention(s) (e.g. 5 terminal half-lives) after the last dose of study intervention:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
    - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception (see Appendix 4) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 1 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. History or presence of cardiovascular, respiratory, hepatic, urological, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
2. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
3. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
4. Current or chronic history of liver disease or known hepatic or biliary abnormalities (except for Gilbert's syndrome or asymptomatic gallstones).
5. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.
6. Exclusion criteria for screening ECG:

	Males	Females
Heart rate	<45 or >100 bpm	<50 or >100 bpm
PR Interval	<120 or >220 msec	
QRS duration	<70 or >120 msec	
QTcF interval	>450 msec	

Notes: A heart rate from 100 to 110 bpm can be rechecked by ECG or vitals within 30 minutes to verify eligibility, and the second reading used if this falls within acceptable limits.

The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

7. Evidence of previous myocardial infarction on ECG (does not include ST segment changes associated with re-polarization).
8. Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], WPW syndrome).
9. Sinus Pauses >3 seconds
10. Any significant arrhythmia which, in the opinion of the Investigator or GSK Medical Monitor, will interfere with the safety for the individual participant.
11. Non-sustained or sustained ventricular tachycardia (3 consecutive ventricular ectopic beats).
12. Current or history of renal disease, or estimated creatinine clearance <90 mL/min/1.73m^2 or serum creatinine >ULN at screening.

Prior/Concomitant Therapy

13. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) 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 study intervention, unless in the opinion of the Investigator and the GSK medical monitor, the medication will not interfere with the study procedures or compromise participant safety.
14. Use of a systemic antimicrobial within 30 days of screening.

Prior/Concurrent Clinical Study Experience

15. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days.
16. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
17. Current enrolment or past participation within the last 30 days before signing of consent in any other clinical study involving an investigational study intervention or any other type of medical research.

Diagnostic assessments

18. Positive human immunodeficiency virus (HIV) antibody test
19. Presence of Hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention.
20. Positive Hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention.

    NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.
21. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention.

NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

22. Positive pre-study drug/alcohol screen
23. Any history of substance abuse or a positive test for drugs of abuse at screening or admission
24. A positive highly sensitive pregnancy test (urine or serum as required by local regulations) at screening.
25. A positive laboratory confirmation of COVID-19 infection, or high clinical index of suspicion for COVID-19.

Other Exclusions

26. Part 1 (Food Effect): Participant must have no dietary restrictions (e.g., lactose intolerance) or inability to eat a high fat meal.
27. Regular alcohol consumption within 6 months prior to the study defined as:

    An average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to approximately (250 ml) of beer, (100 ml) of wine or (35 ml) measure of spirits
28. Positive smoke breathalyzer indicative of smoking history at screening and each in-house admission to the clinical research unit or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening.
29. 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.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Standardized meals will be provided while the participant is confined to the clinical unit. At all mealtimes, food will be served only after the completion of protocol specific procedures.
- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the first dose of the study until after the final dose.
- 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).
- Meals will be provided at approximately 4 hours and 10 hours, respectively, after dosing. A light snack would be at approximately 13 hours post-dose and is finished prior to the overnight 8 hour fast, when fasting is applicable.
- Meals on Day-1 will follow the Day 1 schedule.

5.3.1.1. Fasted Conditions

- In Part 1 (except food effect), participants will fast from food and drink (except water) at least 8 hours prior to dose and no food is allowed until 4 hours post-dosing on Day 1 (Parts 1 and 2) and Day 7 (Part 2 only). Meals at all other times will be provided at times that should not interfere with fasting requirements for clinical laboratory testing. See the study reference manual (SRM) for additional details.

5.3.1.2. Fed Conditions

- For the Food Effect, participants will be fed a standard FDA high fat/high calorie meal after at least 8 hours of fasting and completion of pre-dose assessments (see Table 8 for a description of the standard FDA high fat/high calorie meal.). The meal will be provided approximately 30 minutes prior to administration of study intervention. Study participants must consume the entire meal in 30 minutes or less. Noncompliance will be recorded as well as the amount of the meal not eaten.
- The high fat/high calorie meal provided in the Food Effect should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal will be outlined in the study report. Substitutions in this test meal can be made if the meal provides a similar number of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

Table 8 Standard FDA High Fat, High Calorie Diet

Food	Quantity	Carbohydrate (g)	Protein (g)	Fat (g)	Calories
2 eggs fried in butter	2 eggs / 1 tsp butter	1.2	12.6	10 + 7.6	213
Bacon	2 strips	0	8	10	121
Hash brown potatoes	4 oz	20	3	2	125
Whole milk	8 oz	12	8	8	145
Toast	2 slices	30	5	2	180
Pats of butter	2 tsp	0	0	15.2	136
Total		**58.2**	**36.6**	**53.8**	**920**

These fasting requirements may be removed or modified at the discretion of the sponsor in consultation with the investigator

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants must abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final pharmacokinetic (PK) sample.
- During each dosing session, participants must abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products is not to be allowed from 6 months prior to screening until after the final follow-up visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
- Participants will remain in bed for 4 hours post-dosing on Day 1 (Parts 1 and 2) and Day 7 (Part 2 only).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are 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, 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. Holter monitoring does not need to be repeated for the same participant being rescreened within three months of original screening. Rescreened participants should be assigned a new participant number.

Individuals who meet the eligibility criteria and are reserve participants who are subsequently not required for that cohort, could be used in other groups /later cohorts.

- If reserve participants are still within the screening window (30 days) no need to rescreen or assign a new subject number.
- If reserve participants are outside the screening window the site would reconsent the participant and complete the screening assessments (repeat bloods, ECG ,vitals etc).
- 24-hour Holter Monitor would still be valid if it is completed within 3 months of study start and need not be repeated.

5.5. Self-isolation

Where it is site policy to do so, participants will be asked to attend the Unit a few days prior to admittance to receive a COVID-19 test. Once they have had this test they should be asked self-isolate at home until their admittance to the Unit for their next dosing period.

6. STUDY INTERVENTION

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

	Study Intervention	
Product name:	**GSK3882347**	**Placebo**
Formulation description	Active Pharmaceutical Ingredient	Excipient
Dosage form	Capsule	Capsule
Unit dose strengths/Dosage levels	Active Pharmaceutical Ingredient (API) alone in capsule to be prepared by extemporaneous compounding to required weight. Multiple Capsules can be used as required. Fill weight can span from 11mg to 220mg as required (equates to 10 - 200mg dose)	To match active
Route of Administration	Oral	Oral
Dosing instructions	Study medication will be administered by the study personnel during each dosing day with approximately 240 mL of water	Study medication will be administered by the study personnel during each dosing day with approximately 240 mL of water
Physical description	Powder in capsule	Powder in capsule
Sourcing/Compounding	GSK, Addenbrookes Centre for Clinical Investigation (ACCI), CUC (Clinical Unit Cambridge), to provide blinded, labeled, API in capsule and Placebo capsules via Extemporaneous Compounding	GSK, ACCI, CUC (Clinical Unit Cambridge), to provide blinded, labeled, API in Capsule and Placebo capsules via Extemporaneous Compounding
Packaging and Labelling	Capsules provided in labelled HDPE bottles	Capsules provided in labelled HDPE bottles

6.2. Preparation/Handling/Storage/Accountability

Details on storage, handling, and allowable excursions for GSK3882347 investigational product (IP) and placebo will be provided in the Technical Terms of Supply (TTS).

1. A description of the detailed methods and materials required for preparation of GSK3882347 capsule and placebo are provided in the Technical Terms of Supply (TTS).

2. The capsules will be extemporaneously prepared at GSK, Addenbrookes Centre for Clinical Investigation (ACCI), CUC (Clinical Unit Cambridge) as per instructions in the Technical Terms of Supply (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.

Precaution will be taken to avoid direct contact with the study intervention. A Safety Data Sheet describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be randomized, according to the randomization schedule generated prior to the study by the Statistics Department at GSK. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number, throughout the study. Each participant scheduled to receive study drug will receive a treatment allocation number when randomized. In Part 1(SAD), participants will be randomized in a 3:1 ratio and in Part 2 (MAD), participants will be randomized in a 4:1 ratio to receive study treatment (active drug: placebo). Part 1 will consist of two cohorts with up to a four-period for each cohort. Part 2 will consist of four cohorts for each of the MAD dose (Figure 1).

This will be a double-blind study with participants and the site staff blinded. The sponsor will be unblinded. For dose escalation, the Sponsor study team physicians, statistician, and clinical pharmacokinetic staff and/or their delegate will have access to unblinded data. Other Sponsor staff will remain blinded unless unblinding becomes necessary. The blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The Sponsor study team must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, the Sponsor study team must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

Unblinded monitors, and in the event of a Quality Assurance audit, the auditor(s), will be allowed access to un-blinded study treatment records at the site to verify that randomization/dispensing has been done accurately.

A participant will be withdrawn if the participant's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the 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

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- 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 personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

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

- reason for use
- dates of administration including start and end dates

- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Medication and Non-Drug Therapies

Paracetamol or Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

6.5.2. Prohibited Medication and Non-Drug Therapies

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) 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, unless, in the opinion of the investigator and Medical Monitor, the medication will not interfere with the study. This includes any medications which are substrates of CYP3A4 and sensitive to metabolic induction.

Use of a systemic antimicrobial within 30 days of screening.

6.5.3. Rescue Medicine

It is not anticipated that rescue medication will be required as this is a study in healthy participants.

6.6. Dose Modification

The decision to proceed to the next dose level in both Part 1 (SAD) and Part 2 (MAD) will be made by the GSK study team and study investigator based on safety, tolerability, and preliminary PK data obtained from the prior dose level(s).

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, and PK findings at a given dose level or to add cohorts to evaluate up to 2 additional dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as those described for other study participants/cohorts.

6.7. Intervention after the End of the Study

Not applicable.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued due to an adverse event, the participant will remain in the study to be evaluated for resolution of the event or return of labs to acceptable levels. See the SOA for data to be collected at the time of discontinuation of study intervention.

If a participant withdraws from the study, he/she must complete a follow-up visit.

7.1.1. Gastrointestinal Events (diarrhea or colitis)

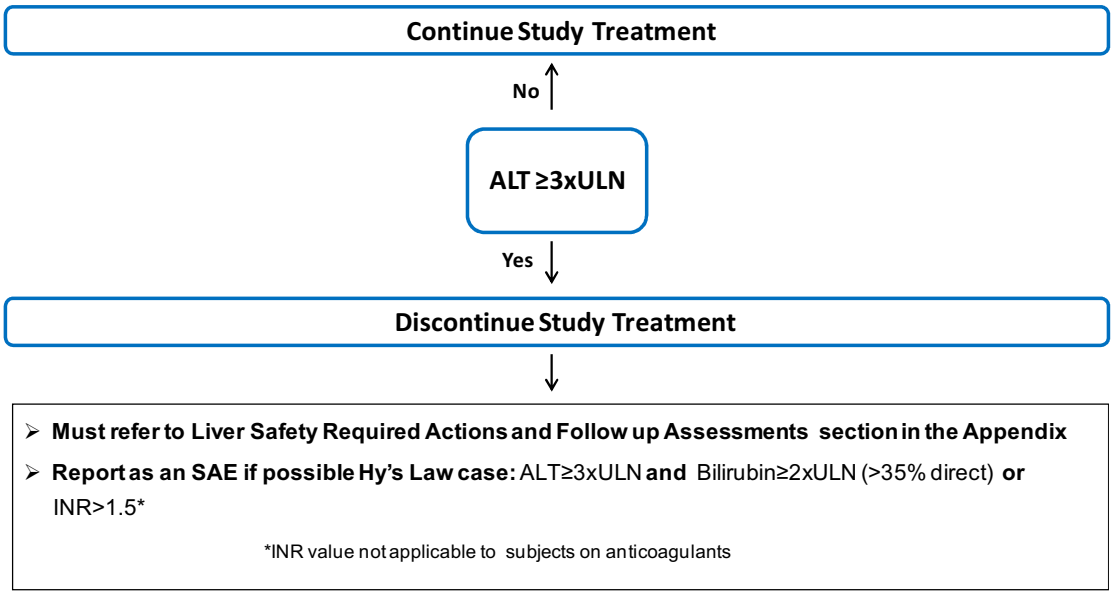
Grade	Diarrhea	Management	Follow-up
Mild **(Grade 1)** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities	Increase of <4 stools per day over Baseline	• Administer antidiarrheal and symptomatic treatment as appropriate • Discuss participant continuation in the trial with Sponsor/Medical Monitor	*Symptoms resolve to baseline within 3 days:* • Provide close follow-up to evaluate for increased severity. *Symptoms ongoing > 3 days*: • Consider following algorithm for Grade 2 events
Moderate **(Grade 2)** An event that causes sufficient discomfort and interferes with normal everyday activities	Increase of 4 - 6 stools per day over Baseline	• Interrupt study drug(s) • Administer antidiarrheal and symptomatic treatment • Investigate etiology; consider consulting GI service • Discuss participant continuation in the trial with Sponsor/Medical Monitor	*Symptoms resolve to ≤ Grade 1 or baseline within 7 days*: • Continue follow-up and evaluate for any increased severity. *Symptoms ongoing > 7 days, blood or mucus in stool, or ulceration/bleeding on endoscopy*:

Grade	Diarrhea	Management	Follow-up
			• Consider following algorithm for Grade 3 events
Severe **(Grade 3-4)** An event that prevents normal everyday activities	**Grade 3**: Increase of ≥7 stools per day over Baseline; incontinence; hospitalisation indicated **Grade 4**: life-threatening consequences; urgent intervention indicated	• Discontinue study drug(s) • Consult GI service • Discuss participant continuation in the trial with Sponsor/Medical Monitor	*Symptoms ongoing:* • Continue follow up of participant • Discuss further management with GI consultant and Sponsor/Medical Monitor

7.1.2. Liver Chemistry Stopping Criteria

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

Phase I 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.

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

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

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

- a participant meets one of the conditions outlined in the algorithm

  OR

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

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

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

7.1.3. QTc Stopping Criteria

- The Fridericia QT correction formula (QTcF) *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 15 minute) recording period.
- A participant that meets either bulleted criterion below will be withdrawn from the study.
  - QTcF > 500msec,
  - Change from baseline: QTcF >60msec

See Section 1.3 for data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.4. Individual Stopping Criteria

- Any participant who experiences an SAE will be withdrawn from the study.
- Any participant who experiences an AE of moderate or severe intensity that is considered attributable to dosing with GSK3882347 will be withdrawn from the study.
- If a participant develops COVID-19 like symptoms during the course of the study the following actions should be taken:
  - During Part 1 (SAD portion of the study), participants who develop a high clinical index of suspicion for COVID-19 disease should be isolated and tested for COVID-19 in accordance with site procedures.
  - During Part 2 (MAD portion of the study), study treatment should be halted for any participants who develop a high clinical index of suspicion for COVID-19 disease; they should be isolated and tested for COVID-19 in accordance with site procedures.
  - In both cases, assessments should be continued as per the protocol during this period; withdrawal of participants from the study will be at the discretion of the Principal Investigator, but should first be discussed and agreed with the GSK Medical Monitor.

7.1.5. Dose Adjustment/Discontinuation Pharmacokinetic Criteria

The exposures observed in animal toxicology studies will be used to guide dose escalation. Systemic exposures in the human participants in this study may exceed the systemic NOAEL animal exposures from 14-day GLP toxicology studies if the doses administered in the study are safe and well tolerated.

For Part 1, the need to dose escalate will be evaluated if no meaningful increase in exposure is observed with an increase in dose (i.e., a plateau in exposures is reached).

7.2. Study Stopping Criteria

In the event of any of the following, ongoing dosing will be halted and no new participants will be dosed at this dose level. A safety review will be undertaken; following this review an additional cohort may be enrolled at a lower dose level.

- An SAE that is related to GSK3882347 in one or more participants on active treatment.
- Two similar AEs of moderate intensity in 2 or more participants.
- Two AEs of severe intensity (but not necessarily similar) in 2 or more participants.
- Finally, if a sentinel participant receiving GSK3882347 meets any of these clinical stopping criteria, the rest of the Period (SAD) or Cohort (MAD) will not be dose and further dose escalation will not occur (see Section 7).

Dosing at the current (higher or lower) dose may resume only following approval of a substantial amendment by the MHRA as well as the ethics committee.

7.3. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted (assessments in the follow-up visit), as shown in the SoA in Section 1.3. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.4. Lost to Follow Up

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

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

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

Discontinuation of specific sites or of the study are handled as part of Appendix 1.

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.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:
    1. 12-lead ECG
    2. Vital signs

3. Urine specimen collections
4. Pharmacokinetic and safety blood draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL in 56 days.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Time window allowances for all study assessments will be followed according to the time window allowances as indicated in the SRM.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points 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.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Vital signs (to be taken before blood collection for laboratory tests) will include tympanic-measured temperature, systolic and diastolic blood pressure, pulse and respiratory rate.
- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- 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) and for at least 10 minutes prior to and 5 minutes after each time point for ECG extractions.

- Vital signs when measured in triplicate in the SoA blood pressure measurements and pulse (3 consecutive readings will be recorded at intervals of at least 1 minute). The average of the 3 readings will be recorded on the CRF.

8.2.3. Holter Monitoring

Approximately 24-hour screening Holter Monitoring will be collected in all participants of the study. The 24-hour Holter Monitoring will be performed to eliminate participants with non-clinically overt cardiac arrhythmias. If necessary, additional or extended monitoring (e.g., telemetry or Holter) may be performed at the Investigator or Sponsor's discretion to further characterize any emerging safety signals.

8.2.4. Electrocardiograms

8.2.4.1. 12-lead safety ECGs

Safety ECGs will be printed and interpreted on-site by the Investigator to ensure participant safety. Safety ECGs may be printed from the Global Instrumentation Holter device (see below). Refer to Section 7 for QTc withdrawal criteria and additional QTc readings that may be necessary (equipment may be used to print out ECG's for scheduled or for AE's). (if have the capability to print out ECGs, may be done). Holter Monitor ECG are collected and held for analysis not in real time. Where there are scheduled ECGs, collection or an AE that requires ECG collection, if the Holter ECG instrumentation allows for a printout of an instantaneous ECG, the Holter equipment may be used to collect.

8.2.4.2. Cardiodynamic assessment (ECGs extracted from Holter recordings)

The frequency of ECG data in the SAD and MAD arises from emerging literature suggesting frequent QT evaluation early in development may mitigate the need for a formal TQT study [Darpo, 2014]. ECGs will be extracted as shown in the SOA from the SAD and the MAD component of the study, not including the extension cohort. Should clinical development of GSK3882347 continue, an exploratory objective of this study is to assess the exposure-response relationship between GSK3882347 and QTcF following single and repeat dose administration.

The 12-lead Holter/ECG equipment will be supplied and supported by ERT. All continuous ECG (Holter) data will be collected using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12-lead digital recorder. The continuous 12-lead digital ECG data will be stored onto SD memory cards. In case the cardiodynamic evaluation is undertaken, 12-lead ECGs will be extracted in replicates from the continuous ECG recording at pre-determined time points as defined in the SOA and will be read centrally by ERT.

The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the participant, visit and treatment allocation
- Baseline and on-treatment ECGs for a participant will be over-read on the same lead and will be analyzed by the same reader.

- The primary analysis lead is lead II. If lead II is not analyzable in any specific participants, then primary lead of analysis will be changed to another lead for the entire participant data set.

Additional details can be found in the SRM.

8.2.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 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 such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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

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

- All SAEs will be collected from the signing of the informed consent form until the follow-up visit at the time points 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 subject consents to participate in the study.
- All AEs will be collected from the start of intervention until [the follow-up visit] at the time points specified in the SoA (Section 1.3).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 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 AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading 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 7.4). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a 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, Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected where conception may have occurred during or up to 5 days after dosing.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

For this study, any dose of GSK3882347 greater than 900 mg within a 24-hour time period (±1 hour) will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3882347 can no longer be detected systemically (at least 5 days).
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the 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.

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection

- Whole blood samples of approximately 1 mL will be collected for measurement of plasma concentrations of GSK3882347 as specified in the SoA. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. A maximum of 10 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

- A 1 mL of whole blood sample will be collected for metabolite profiling on Day 1 in Part 1 (excluding food effect groups); and 4 mL in Part 2 as specified in the SoA.
- The metabolite profiling of the plasma samples will be conducted under separate protocols and results are reported separately according to the IV/IVT DMPK, GSK protocols.
- 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 IV/IVT, GSK protocols.
- Genetic analyses will not be performed on these whole blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained. Participant confidentiality will be maintained. At visits during which whole blood samples for the determination of GSK3882347 will be taken, one sample of sufficient volume can be used.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Details of blood sample processing, storage and shipping procedures are provided in the SRM or equivalent.

8.5.2. Urine Sample Collection

- Urine samples will be collected up to 96 hours from dosing in Part 1 and up to 24 hours from dosing on Days 1 and 7 in Part 2 MAD (exact times are specified in the SoA). The time will be recorded for each urine sample collected, and the total urine volume for each subject 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. **Note: it is highly important that the urine sample is thoroughly mixed using several repeat inversions of the sample *prior* to removal of the 1 mL aliquot for PK analysis.**
- The metabolite profiling of the urine samples will be conducted under separate protocols and results are reported separately according to the IV/IVT DMPK, GSK protocols.
- The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of urine sample processing, storage and shipping procedures are provided in the SRM.

8.6. Plasma Sample for CYP3A4 Enzyme Activity

Plasma derived from 3 mL blood samples in Part 2 (as in the SoA Table, see Section 1.3) will be analyzed for 4β-hydroxycholesterol and cholesterol as a potential *in vivo* marker of CYP3A4 enzyme activity.

Details on CYP3A4 enzyme activity marker plasma sample collection, processing, storage and shipping procedures are provided in the SRM.

Plasma samples collected in the fasted state at Baseline and on Day 8 (i.e. collected 24 hours post dosing on Day 7) will be analyzed using a validated, specific, and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method to determine concentrations of 4β-hydroxycholesterol and total cholesterol. A comparison will be made between the ratio of 4β-hydroxycholesterol: cholesterol at baseline and on Day 8 to assess potential changes in CYP3A4 enzyme activity following GSK3882347 treatment.

Analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of PTS-IVIVT and Third Party Resource, GlaxoSmithKline.

8.7. Pharmacodynamics

8.7.1. Microbiome Assessments

Stool specimens for potential microbiome assessment will be obtained at the time points as specified in the SoA. The actual date and time of each sample collection will be recorded.

Collection, processing, storage, and shipping procedures for microbiome specimens are provided in the Central Laboratory Manual.

8.8. Genetics

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

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

See Appendix 5 for Information regarding genetic research. Details on processes for collection and shipment can be found in the Central Laboratory Manual and destruction of these samples can be found in SRM.

8.9. Biomarkers

Biomarkers are not evaluated in this study.

8.10. Health Economics/Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by, or under the direct auspices of, Biostatistics, GlaxoSmithKline.

Reporting of study data will be performed in accordance with applicable GSK and/or contract research organization (CRO) standards.

Complete details of the planned statistical analyses will be provided in the Reporting and Analysis Plan (RAP).

Any deviations from the planned analyses will be described in a RAP addendum and justified in the final integrated clinical study report.

9.1. Statistical Hypotheses

No formal statistical hypotheses will be tested.

9.2. Sample Size Determination

Approximately 56 randomized participants will be recruited for the entire study, including 16 evaluable participants in the SAD part (Part 1) with 6 active and 2 placebo per cohort, and 40 evaluable participants in the MAD part (Part 2) with 8 active and 2 placebo per cohort. Additional participants may be recruited as replacement for withdrawn participants including those for COVID-19.

A preliminary PK/PD target was determined as a trough GSK3882347 urine concentrations in the range of 5 to 30 µM, where 5 µM represent the minimum trough concentration potentially associated with efficacy in the clinic.

Since this is a first in human study, sample size justification is based on data predicted from animal studies. Table 9 and Table 10 contain the predicted human urine trough concentration based on dog and rat PK data under 4 dose levels and 3 urine volumes. The assumption is the urine trough concentration follows log-normal distribution with mean value listed in Table 9 and Table 10. The probabilities of successfully achieving ≥5 µM in urine under each setting are presented in Table 11 and Table 12.

Table 9 Human Urine Trough Concentration Predicted From Dog PK Data

Dose (mg)	Avg urine vol	Low urine vol	High urine vol
900 QD	93.6	151.6	60.6
500 QD	65.6	106	42.5
150 QD	20.9	33.8	13.5
50 QD	6.94	11.2	4.5

Table 10 Human Urine Trough Concentration Predicted From Rat PK Data

Dose (mg)	Avg urine vol	Low urine vol	High urine vol
900 QD	30.6	49.6	19.8
500 QD	10.7	17.3	6.91
150 QD	1.37	2.22	0.888
50 QD	0.422	0.684	0.274

Table 11 Probability (%) of All 8 Participants (90%) Achieving Urine Trough ≥ 5μM PK Based on Dog Data

Dose (mg)	Avg urine vol	Low urine vol	High urine vol
900 QD	98.16	99.59	93.77
500 QD	95.24	98.59	85.14
150 QD	49.86	76.36	22.78
50 QD	2.22	14.44	0.25

*SD of 1.04 from study 206899 is used as the SD of log transformed data.

Table 12 Probability (%) of All 8 Participants (90%) Achieving Urine Trough ≥ 5μM PK Based on Rat Data

Dose (mg)	Avg urine vol	Low urine vol	High urine vol
900 QD	71.8	89.3	46.1
500 QD	11.8	37.1	2.1
150 QD	0	0	0
50 QD	0	0	0

*SD of 1.04 from study 206899 is used as the SD of log transformed data.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Randomized	All participants who passed screening and were randomized into the study. Note: Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.
Safety	All participants who received at least 1 dose of study intervention. Participants will be analyzed according to the treatment they received. Note: Participants who were not randomized but received at least one dose of study intervention should be listed.
Pharmacokinetic (PK)	All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).

9.4. Statistical Analyses

9.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population and details will be provided in the Reporting and Analysis Plan (RAP).

Endpoint	Statistical Analysis Methods
Adverse events (AEs)	The proportion of participants reporting AEs will be tabulated by study intervention and by cohort. AEs will also be tabulated by severity and relationship. AEs will be tabulated using MedDRA preferred terms. The number and percentage of participants experiencing each specific AEs (All AEs, Grade 2 or higher, and SAEs) will be tabulated by severity and by relationship to study product. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity or the strongest relationship to study product. AEs leading to withdrawal will also be summarized by study intervention.
Clinical laboratory	Laboratory results will be included in the reporting of this study for haematology, clinical chemistry and urinalysis. Based upon laboratory normal ranges, the laboratory test results will be categorized according to the normal range as low (below the lower limit), normal (within the normal range) and high (above the upper limit). Summary statistics for change from baseline will also be tabulated.
Vital signs assessments	The following Vital Signs measurements will be tabulated: semi-supine systolic and diastolic blood pressure, pulse rate, respiratory rate and tympanic temperature. Summary statistics for change from baseline will also be tabulated.

9.4.2. Pharmacokinetic Analyses

All pharmacokinetic analyses will be performed on the Pharmacokinetic Population. For the secondary pharmacokinetic (PK) endpoints in this study, no formal hypotheses will be tested.

Endpoint	Statistical Analysis Methods
Primary	Plasma GSK3882347 concentration-time data will be analysed by non-compartmental methods using WinNonlin Professional 5.2 or higher, Phoenix (Pharsight Corporation) or comparable software. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: **Part 1 (single dose)**: AUC(0-24), AUC(0-t), AUC(0-∞), Cmax, C24h, tmax, tlag and t1/2 of GSK3882347 **Part 2 (repeat dose)**: AUC(0-tau), Cmax, tmax and Ctau of GSK3882347 Amount excreted in urine (Ae) of unchanged GSK3882347, fraction of the dose excreted in urine (fe) and renal clearance (CLr)
Secondary	**Part 1 (single dose)**: Dose proportionality will be assessed by visual inspection of dose normalised AUC(0-∞) [or if not available AUC(0-t)] and Cmax values versus dose. Analysis of these $\log_e$-transformed parameters may be carried out, using the power model. **Part 2 (repeat dose)**: The extent of accumulation after repeat dosing, the observed accumulation ratio, may be determined. Accumulation indices for PK parameters assessed across first and last doses of multiple dosing, as data allow: RAUC(0-tau), RCmax, RCtrough. For repeat dosing, AUC(0-tau), Cmax, Ctrough will be analyzed versus dose for the dose-proportionality. **Food Effect**: AUC(0-24), AUC(0-t), AUC(0-inf), C24h, Cmax, tmax and tlag will be evaluated. Further details will be included in the RAP.

9.4.3. Other Analyses

PK and exploratory analyses will be described in the reporting and analysis plan. The population PK analysis will be presented separately from the main clinical study report (CSR).

9.5. Interim Analyses

There will be no formal statistical interim analysis. However, preliminary safety, and PK data will be reviewed in-stream by the GSK study team members prior to each dose escalation. Data for these reviews will be cumulative and can include individual participant data, summaries by study intervention and graphical displays. This is a sponsor unblinded trial and GSK staff will be unblinded for these reviews (see Section 9.5.1).

Preliminary results from available safety data may be reported prior to database freeze for the purposes of safety review by GSK, and where required by regulatory bodies. Other selected preliminary data may be unblinded and reported prior to database freeze for internal decision making.

In each case described above, the study will not be officially unblinded and access to the randomization will be restricted.

The dose escalation plan will describe the planned dose escalation analyses in greater detail.

9.5.1. Dose Escalation Committee (DEC)

A Dose Escalation Committee (DEC) will be responsible for ongoing monitoring during the study.

A DEC consisting of the following members including but not limited to the Principal Investigator, GSK Medical Monitor, GSK Clinical Scientist Lead, GSK Discovery Medicine Lead, GSK Pharmacokineticist, GSK Safety and Medical Governance Representative, GSK Statistician, GSK Study Delivery Lead and GSK Data Quality Lead will review available data from all participants in each cohort; and before initiating each new dose level in a minimum of four participants who received active treatment in the previous cohort in Part 1 and at least 7 days of repeat dosing in a minimum of five participants who received active treatment in the previous cohort in Part 2. Dose escalation may occur only after review of the following data:

- Part 1: Up to Day 2 (24 hours) post-dose for PK and Day 5 (96 hours) post-dose for safety
- Part 2: Up to Day 8 (24 hours post-Day 7) for safety and PK

The data may be reviewed in an unblinded fashion by the unblinded members of the DEC should a safety concern arise during the blinded review. These unblinded members will be defined within the Dose Escalation Plan.

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, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IEC by the investigator and reviewed and approved by the IEC before the study is initiated.
- Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
  - Notifying the IEC of SAE or other significant safety findings as required by IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IEC, European regulation 536/2014 for clinical studies (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 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 to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

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

10.1.5. Committees Structure

This study will utilize a Dose Escalation Committee (DEC) made up of the at least the following members including but not limited to the Principal Investigator, Medical Monitor, GSK Study Team Leader, GSK Pharmacokineticist, Safety and Medical Governance Representative, GSK Statistician, Operational Study Lead and Data Quality Lead. The committee will evaluate data including but not limited to: AEs, vital signs, laboratory findings, ECG parameters, and PK data.

Dose escalation decisions will be made as outlined in Section 9.5.1 and in the Dose Escalation Plan.

10.1.6. 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.

10.1.7. Dissemination of Clinical Study Data

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

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9. Source Documents

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

10.1.10. Study and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs, 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 subject and should assure appropriate subject therapy and/or follow-up.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- 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.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 13 Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
• MCV
• MCH
• %Reticulocytes and ratio (Reticulocyte Index [RI])</td><td>WBC count with Differential:
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils</td></tr>
<tr><td rowspan="3">Clinical Chemistry[1]</td><td>BUN</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine[3]</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose fasting)</td><td>Calcium</td><td>Alkaline phosphatase</td><td></td></tr>
<tr><td>Urine chemistry</td><td colspan="4">Creatinine from 24-hour urine sample</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• Specific gravity
• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick</td></tr>
</table>

Laboratory Assessments	Parameters
	• Microscopy (in the presence of clinically significant amount of blood (e.g. > +10) by dipstick) • Protein/creatinine ratio (in the presence of clinically significant protein e.g. > trace) in urine by dipstick)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Breath alcohol and urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines • Smoke breathalyzer • Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed)[2] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C antibody) • COVID-19 testing (performed at additional time noted in the SoA tables and as required) The results of each test must be entered into the CRF.

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 Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IEC.
3. eGFR will be derived from serum creatinine using the Cockroft-Gault formula.

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

Laboratory/analyte results will utilize local standard testing (i.e. serum or plasma) for the protocol lab assessments, as appropriate.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study 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.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

- Results in death
- Is life-threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils 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.

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that

may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

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

10.3.4. Reporting of SAE to GSK

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

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF 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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Study Reference Manual.

10.4. Appendix 4: Woman of Nonchildbearing Potential (WONCBP) Guidance

10.4.1. Definition

Woman of Childbearing Potential (WOCBP)

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

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.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - 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), 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.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.

10.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the 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.*
• **Highly Effective Methods[b] That Are User Dependent**

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

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

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

10.4.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to male participants who receive GSK3882347.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to GSK3882347 and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3882347, and recurrent uncomplication urinary tract infection. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to 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 recurrent uncomplication urinary tract infection 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 I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, 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
If ALT≥3xULN AND bilirubin < 2xULN and</td><td colspan="2">• Viral hepatitis serology[3]
• Obtain international normalized ratio (INR) and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 7 days of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• 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 AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form</td></tr>
</table>

Liver Chemistry Stopping Criteria	
INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, 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	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • 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 high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. 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: Country-specific requirements

No country-specific requirements exist.

10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

ACCI	Addenbrookes Centre for Clinical Investigation
AE	adverse event
Ae	amount excreted in urine
ALT	alanine aminotransferase
API	Active Pharmaceutical Ingredient
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-∞)/ AUC(0-inf)	AUC extrapolated from time zero to infinity
AUC(0-τ)	AUC over the dosing interval τ
AUC(0-12)	AUC from time zero to 12 hours after dosing
AUC(0-24)	AUC from time zero to 24 hours after dosing
AUC(0-t)	AUC from time zero to the last quantifiable concentration after dosing
BP	blood pressure
CL	total systemic clearance
CI	confidence interval
CLr	renal clearance
Cmax	maximum plasma concentration
COVID-19	Coronavirus Disease 2019
C24	plasma concentrations at 24 hours after dosing
Ctau	plasma concentrations over the dosing interval τ
Cτ	trough concentration
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FaSSIF	Fasted-state simulated intestinal fluid
FDA	Food and Drug Administration
Fe	fraction of drug excreted in urine
FeSSIF	Fed-state simulated intestinal fluid
Feu(t1-t2)	urinary excretion ratio relative to dose
FSH	follicle-stimulating hormone
FTIH	first time in human
GCP	Good Clinical Practice
GRF	Glomerular filtration rate
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
hCG	human chorionic gonadotropin
HED	human equivalent dose
Hgb	Hemoglobin
Hct	Hematocrit

HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
INR	international normalized ratio
Kg	Kilogram
L	Liter
µg	Microgram
MABEL	Minimal Anticipated Biological Effect Level
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MHRA	The Medicines and Healthcare Products Regulatory Agency
mL	Millilitre
mm Hg	millimeters of mercury
MRSD	maximum recommended starting dose
MRT	mean residence time
Msec	Millisecond
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBPK	physiologically based pharmacokinetic
PK	Pharmacokinetic
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
SAD	single ascending dose
SAE	serious adverse event
SRM	study reference manual
RAP	reporting and analysis plan
RBC	red blood cell
Ro	observed accumulation ratio
rUTI	Recurrent urinary tract infections
t1/2	terminal elimination half-life
tlag	lag time
Tmax	time to Cmax
TTS	Technical Terms of Supply
ULN	upper limit of normal
UTI	Urinary tract infection
Vd	volume of distribution
Vd/F	Apparent volume of distribution after non-intravenous administration
WBC	white blood cell

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
Phoenix (Pharsight Corporation)
WinNonlin

10.9. Appendix 9: COVID-19 Appendix

10.9.1. Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until study completion.

10.9.2. Study Procedures During COVID-19 Pandemic

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

As outlined in Section 8, Protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.9.3. Protocol Defined Procedures/Visits:

- The protocol defined interval for the collection of samples during the follow-up visit (see Section 1.3 Schedule of Activities), may be extended up to a maximum length of 14 days.
- If visits to a site are not feasible, then the medical evaluation of safety may take place by phone calls as a way of communicating with and monitoring the participant.

- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via phone call.
- The participant should be informed of the plan and any potential risks associated with review of information by site monitors in alternative ways other than during in person visits (i.e. phone calls with the site staff or viewing documents remotely during secure web or in systems where documents can be uploaded) and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

10.9.4. Data Management/Monitoring:

- If a situation arises where on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK

10.10. Appendix 10: Protocol Amendment History

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

Amendment 1 (02-JUN-2020)

Overall Rationale for Amendment 1: This amendment includes revisions to the reporting of the primary endpoint, eligibility criteria, including decrease in creatine clearance and screening for COVID-19, COVID-19 related activities, removal of PCI for extemporaneous compounding, procedural changes in-line with clinical site, minor clarifications and consistency corrections, formatting corrections.

Section # and Name	Description of Change	Brief Rationale
1.1 & 3 Objectives and Endpoints	Changed reporting of the primary endpoint	To align with new reporting guidelines
1.1 Synopsis 4.1 Overall Design	Mentioned in Part 1, that food effect evaluation will be conducted in last period	Included in these sections for completeness
1.3 SoA Tables 2.3.2 Risk Assessment 5.2 Exclusion Criteria 5.5 Self Isolation 7.1.4 Individual Stopping Criteria 7.3 Withdrawal Criteria 9.2 Sample size determination Appendix 10 COVID-19 Appendix	Addition of COVID-19 to eligibility criteria, adjustment of age limit, risk and mitigations, screening and monitoring to SoA tables, additional COVID-19 testing based on clinical presentation during discharge, participant stopping criteria, withdrawal criteria, replacement of participants including due to COVID-19 and appendix	In light of the COVID-19 pandemic, GSK anticipates that many ongoing studies will receive cases of suspected or confirmed COVID-19 infections and plans to implement procedures within the clinical trials for monitoring
1.3 SoA Tables 8.2.2 Vital Signs	Positioning and timing of Vital Signs	Consistent positioning throughout to avoid any conflicts in timing of assessments
1.3 SoA Tables 8.2.2 Vital Signs	Modified method of assessing temperature. Changed oral to tympanic temperature	Preferred method of assessment of temperature for clinical site
1.3 SoA Table	Added Urine Drug, Smoke Breathalyzer and Alcohol Breath Tests to Screening and Day-1 Added Urine Drug, and Alcohol and Smoking Breath Tests to Day-1 Added β-hCG Pregnancy Testing (as appropriate) to Day-1	To ensure compliance with protocol requirement Pregnancy testing as appropriate since only women of non-childbearing potential may participate

Section # and Name	Description of Change	Brief Rationale
1.3 SoA Table	Permissible window included for the Follow-up Visit	Protocol omission. A permitted ± 3 days window around the Follow-up Visit (i.e. 14 days ± 3 days) should have been included
1.3 SoA Table 8.2.3 Holter Monitoring	Added 24-hour Holter Monitoring at screening	Site specific preference
1.3 SoA Tables	Modified timing of sample collection for Genetic analysis	To allow collection of sample at a time point when consent is signed, and participant qualify on the basis of labs and inclusion/exclusion criteria
1.3 SoA Tables	Clarification of stool microbiome collection times	Last sample to be collected close to the last day of discharge to accommodate routine bowel habits
1.3 SoA Tables 2.3.2 Risk Assessment	Clarity of stool type assessment for all bowel movements by Bristol Stool chart	Aid with identification of gastrointestinal adverse effects
1.3 SoA Tables 5.3.1 Meals and Dietary Restrictions	Presentation of meal times adjusted in tables Added meals schedule for Day -1	Minor clarifications. Standardized meals will be provided per site local practices
1.3 SoA Table	IP administration removed from Day 8 – Table 4	Minor error. There will be no administration of study intervention on Day 8 as there is only seven (7) days of dosing and the last dose is on Day 7
1.3 SoA Table	Urine PK collection times in SAD (Part 1) and MAD (Part 2)	Protocol inconsistency. Interval for urine PK collection times to be similar
4.3 Dose Justification	Removal of the reference to the unqualified impurity (RRT1.16)	Specification no longer dose limits up to 900mg
5.2 Exclusion Criteria	Changed estimated creatinine clearance to <60 mL/min/1.73m^2	Normal creatinine clearance levels may vary (GFR category: Grade 1 and Grade 2). In the absence of kidney disease, neither Grade 1 and Grade 2 fulfil the criteria of CKD

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 10.2 Clinical Laboratory Tests	Change to smoke Breathalyzer Test at screening	Removed urine cotinine tests as there can be false positives
5.3.3 Activity	Modified abstain from strenuous exercise for 48 hours	Effect of short term strenuous exercise on laboratory values was extended due to variability in parameters returning to baseline
5.4 Screen Failures	Clarification of screen failure for reserve participants	Modified to allow reserve participants to be rescreened. Reserve participants who met eligibility criteria are categorized as screen failure if not selected for cohort
6 Study Intervention	Removal of PCI	PCI will no longer be responsible for extemporaneous compounding and replaced with Clinical Unit Cambridge
8.2.4.1 12-lead safety ECGs	Replaced abbreviations HM = Holter Monitor and RT = real time	Protocol clarification
8.5.1 Blood Sample Collection	Increase blood volume for metabolite PK samples, Part 2 only	Ensure adequate sample in the event of reanalysis
8.5.2 Urine Sample Collection	Added details on volume of urine to be aliquoted and storage condition for sample	For clarity
8.7 Genetics	Added details that process for genetics samples collection and shipping can be found in the Central Laboratory Manual	For more clarity
9.5.1 Dose Escalation Committee (DEC)	GSK Study Team Leader has been replaced by Clinical Scientist Lead and GSK Discovery Medicine Lead, GSK Study Operational Lead has been replaced by Study Delivery Lead	Revised positions

Section # and Name	Description of Change	Brief Rationale
10.1.3 Informed Consent Process	Removed text on consent form Legally Authorized Representative	The study is in healthy adult participants
10.2 Clinical Laboratory Assessments	Protein/creatinine ratio to be used to investigate proteinuria For Urinalysis, microscopy will be performed by dipstick (in presence of clinically significant amount of blood [e.g. > +10]) Added reticulocyte index (calculated value) COVID-19 testing	Urinalysis - small amount of protein can be found in urine Urinalysis - small amount of blood can be found in urine Reticulocyte count monitoring to help with differential diagnosis COVID-19 testing for screening
10.4.2 Contraception Guidance	Added mandatory use of male condoms for contraception to footnote	Prior omission from footnote
10.8 Abbreviations	Remove IVRS/IWRS system from list of abbreviations Added TTS	IVRS will no longer be used in study Details of IP and placebo storage will be provided in Technical Terms of Supply (TTS)
10.1.9 Source Documents 6.2 Preparation/Handling/ Storage/Accountability	Protocol inconsistencies	Source data definition is normally specified in the source data agreement, removed reference to SRM Material Safety Data Sheet is now Safety Data Sheet

Amendment 2 (10-JUL-2020)

Overall Rationale for the Amendment 2: This amendment is in response to questions raised in the MHRA's Grounds for non-acceptance letter which was received on the 02/07/2020 and includes revisions to the overall design (in-house stay for Part 2), boundaries for dose adjustment, justification of maximum dose, exclusion criteria, gastrointestinal events, and individual/study stopping criteria.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.3 SoA (Table 4) and 4.1 Overall Design	Modified in-house stay for participants in the clinical unit for Part 2	Based on the expected half-life, participants will be discharged from the clinical unit could be 5 days or 5 half-lives (whichever is longer based on the emerging data from Part 1)
1.3 SoA (Table 4)	Addition of assessments on days 9-12 including discharge assessments moved from Day 8 to days 9 through 12. Also meal will be provided until discharge.	Due to the extending in-house stay within clinical unit
2.3.2 Risk Assessment	Modified gastrointestinal toxicity risk	Impacted by modifying management of gastrointestinal toxicity in Section 7.1.1
4.3 Justification for Dose	Added exposure limits	To define the highest permitted dose with regards to exposure
1.1 Synopsis, 4.3.1 Starting Dose	Added boundaries for dose adjustments	To clarify boundaries for adjustments
5.2 Exclusion Criteria	Criteria #12 - Changed estimated creatinine clearance to 90 mL/min/1.73m^2 or serum creatinine >ULN at screening	To reflect healthy participant population
5.2 Exclusion Criteria	Removed Exclusion Criterion #29	Already covered under Inclusion Criteria #4
7.1.1 Gastrointestinal Events (diarrhea or colitis)	Defined grading and modified the management of gastrointestinal toxicity	Severity grading (1-4) required defining
7.1.4 Individual Stopping Criteria and 7.2 Study Stopping Criteria	Deleted references to CTCAE	Intensity of adverse events are assessed using mild, moderate and severe terminology is acceptable for a healthy participant study
7.2 Study Stopping Criteria	Removed requirement for adverse events of severe intensity to be similar, while maintaining two similar moderate adverse events	Two severe adverse events in 2 or more healthy participant must result in the study stopping, regardless of the type of reaction

Section # and Name	Description of Change	Brief Rationale
7.2 Study Stopping Criteria	Addition of text of resumption of dosing after the study stopping criteria have been triggered will require approval of a substantial amendment by the MHRA as well as the ethics committee	To align with the Medicines and Healthcare Products Regulatory Agency (MHRA) guidance for substantial amendment

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	*10-Jul-2020*	*2019N400733_02*
Amendment 1	*02-Jun-2020*	*2019N400733_01*
Original Protocol	*05 -Nov-2019*	*2019N400733_00*

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