TITLE PAGE

Protocol Title: A Three-Part FTIH Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Repeat Oral Doses of GSK3439171A, in a Randomized, Double-Blind (sponsor unblinded), Placebo-Controlled, Dose Escalation study and to Evaluate the Effect of Food on a Single Oral Dose of GSK3439171A in Healthy Adult Participants

Protocol Number: 209275/ Amendment 03

Compound Number: GSK3439171

Study Phase: Phase 1

Short Title: FTIH Study to evaluate the safety, pharmacokinetics, and pharmacodynamics of single and repeat doses of GSK3439171A in healthy participants; food effect

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

05/09/2019

David Neil, MD MFPM
Clinical Director, MM-DPU, FPD

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 3	*09-MAY-2019*	*2018N361438_05*
Amendment 2	*13-MAR-2019*	*2018N361438_04*
Republishing - Amendment 1	*31-AUG-2018*	*2018N361438_03*
Republished - Amendment 1	*29-AUG-2018*	*2018N361438_02*
Amendment 1	*27-AUG-2018*	*2018N361438_01*
Original Protocol	*3-JUL-2018*	*2018N361438_00*

Amendment 3: 09-MAY-2019

Overall Rationale for the Amendment: Part B has been updated with an additional subpart to examine repeat doses of GSK3439171 for a shorter duration at higher exposures. This will help characterize the PK and safety at higher exposures corresponding to the predicted therapeutic dose. The IC50 of GSK3439171 has also been updated to correct the minute typographic error in the ng/mL value as per the human HPGDS enzyme assay. Minor editorial changes have also been made in the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis- Rationale	Addition of 7 day dosing cohort in Part B	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration
1.3 Schedule of Activities	Addition of SoA for 7 day repeat dosing period	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration
2.3.1 Risk Assessment	Updated to reflect changes in exposure limits	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration
3 Objectives and Endpoints	Addition of Ctrough samples during 7 day dosing period	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Clarification of discharge days due to 7 Day repeat dosing.	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration
4.3 Justification of Dose	Updated to reflect changes in increased exposure limits	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration
4.3 Dose Justification	Update for consistency of units (ng/mL) based on the human HPGDS enzyme assay	GSK3439171 concentrations will be reported in units (ng/mL) and based on the corrected human HPGDS enzyme assay, IC50 is 7.77 ng/mL which was previously written in a minor error.
6.6 Dose Modification	Updated language to reflect increased exposure limits for 7 day dosing	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration.
7.1 Dose Discontinuation	Updated language to reflect increased exposure limits for 7 day dosing	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration.
9.4 Statistical Analysis	Addition of days due to 7 day dosing cohort in Part B	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration.
Throughout	Updated language to align to addition of 7 day dosing in Part B	7 Day repeat dosing will be performed in Part B to characterize PK and safety of GSK3439171 at higher exposures for a shorter duration.

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Three-Part FTIH Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Repeat Oral Doses of GSK3439171A, in a Randomized, Double-Blind (sponsor unblinded), Placebo-Controlled, Dose Escalation study and to Evaluate the Effect of Food on a Single Oral Dose of GSK3439171A in Healthy Adult Participants

Short Title: FTIH Study to evaluate the safety, pharmacokinetics, and pharmacodynamics of single and repeat doses of GSK3439171A in healthy participants; food effect

Rationale: The FTIH study with GSK3439171A will evaluate the safety of GSK3439171A in healthy participants in order to avoid confounding factors due to the disease or concomitant drugs in patients. The study design is based on pre-clinical findings for GSK3439171A, contributing to the frequency, type and duration of safety assessment and monitoring during treatment periods in each cohort.

The single dose assessments in Part A will be conducted to determine safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) 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 information. Part A will also serve to identify a dose for use in examining the effect of food on GSK3439171A exposure in Part C.

In Part B, a single dose safety, tolerability and PK will be collected followed by progression of these participants to the repeat dose portion of the study. The up to 14-day dosing was chosen as it is thought to provide sufficient safety and tolerability data to bridge to longer duration studies. The dosing period can be adjusted depending on PK and PD data collected in Part A of the study. Part B will involve more detailed PK/PD/metabolite assessments to better understand the impact of GSK3439171A on target engagement and metabolism in humans. In addition, based on the PK obtained in Part A, an additional cohort will be enrolled to study higher exposures of GSK3439171A for a shorter duration of time.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess the safety and tolerability of GSK3439171A following single and repeat doses in healthy participants	• Adverse events (AE), clinical laboratory values, vital signs, and electrocardiograms (ECG)
• To characterize the PK of GSK3439171A, following single and repeat doses in healthy participants	• Derived PK parameters for GSK3439171A including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-inf), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (t_{max}), and apparent terminal half-life ($t_{1/2}$) as appropriate
Secondary	
• To assess the effect of food on the PK of GSK3439171A following an oral dose in healthy participants	• Derived PK parameters for GSK3439171A including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-inf), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), and apparent terminal half-life ($t_{1/2}$) as appropriate
• To assess preliminary dose proportionality of GSK3439171A following single and repeat oral doses, as data permit	• AUC(0-t), AUC(0-inf), and Cmax following single dose and AUC(0-τ) and Cmax following repeat dose for the assessment of dose proportionality

Objective	Endpoint
• To examine the extent of accumulation and achievement of steady-state following repeat oral doses of GSK3439171A, as data permits	• Determine observed accumulation based on AUC(Ro) and Cmax (RCmax) and determine the steady-state ratio (Rss) • Trough plasma concentrations at the end of the dosing interval (C_τ) collected pre-dose for repeat doses 3, 4, 12, 13, and 14 (or repeat doses 3,4, 6, and 7 during 7 day repeat dosing period) to assess the achievement of steady-state of GSK3439171A.
Exploratory	
• To evaluate the PD properties of GSK3439171A	• Levels of mediators on prostaglandin and/or inflammatory metabolic pathways such as, but not limited to, PGD2, and PGE2.
• To assess the effect of GSK3439171A on QTc in healthy adult volunteers	• Holter monitor data collection and storage for evaluation of the correlation between plasma levels of GSK3439171A and changes in the QTc interval in the future, if appropriate
• To evaluate additional biomarkers of GSK3439171A target engagement after single and repeat doses.	• Levels of change in novel biomarkers in blood, muscle, or urine, such as, but not limited to, urine tetranor PGDM and PGEM (tPGDM, tPGEM), PGD2, and PGE2
• To investigate the plasma, urinary and biliary (Part B) metabolic pathways of GSK3439171A in healthy subjects.	• GSK3439171A-related material in plasma, urine and bile

Overall Design:

Part A is a randomized, double blind (sponsor unblinded), placebo-controlled, crossover, single dose escalation study in healthy participants. Participants will be randomized to placebo or active study intervention groups after screening.

Part B is a randomized, double blind (sponsor unblinded), placebo-controlled, parallel group, repeat dose escalation study in healthy participants. Participants will be randomized to placebo or active study intervention groups after screening.

Part C is a randomized, open label, crossover, food effect study in healthy participants. Participants will be randomized to fed or fasted groups after screening.

Disclosure Statement:

Part A is a Crossover group single ascending dose study with 2 arms per cohort that is participant and investigator blinded.

Part B is a Parallel group repeat dose study with 2 arms per cohort that is participant and investigator blinded.

Part C is a Crossover group food effect study with 2 arms per cohort that is not-masked.

Number of Participants:

Approximately 150 participants will be screened to achieve 75 randomly assigned to study intervention and 75 evaluable participants for an estimated total of 27 evaluable participants in Part A, 36 evaluable participants in Part B, and 12 evaluable participants in Part C. Additional participants/cohorts may be enrolled to allow for evaluation of additional dose levels.

Intervention Groups and Duration:

Part A will be a double-blind (sponsor unblinded), single oral dose, dose-rising, placebo-controlled, randomized (with respect to placebo allocation), 3 period crossover study in approximately 3 cohorts of participants. Participants will be enrolled in the study for approximately 10 weeks (approximately 30 days screening, 3 in-house dose assessment periods of approximately 6 days, 3 wash out periods between each dose of approximately 7 days and an approximately 14 day follow-up period).

Part B will be double-blind (sponsor unblinded), up to 14 day repeat oral dosing, placebo-controlled, randomized (with respect to placebo allocation), dose escalation study with at least three (single or twice-daily) repeat dose levels in 3 separate cohorts of participants who were not enrolled into Parts A or C of this study. Participants will be enrolled in the study for approximately 9 weeks (approximately 30 days screening, approximately 15-22 day in-house dose assessment period, and an approximately 14 day follow-up period.

Part C will be an unblinded, randomized, crossover study where a single dose will be administered fasted or fed conducted in a separate cohort of participants than those who

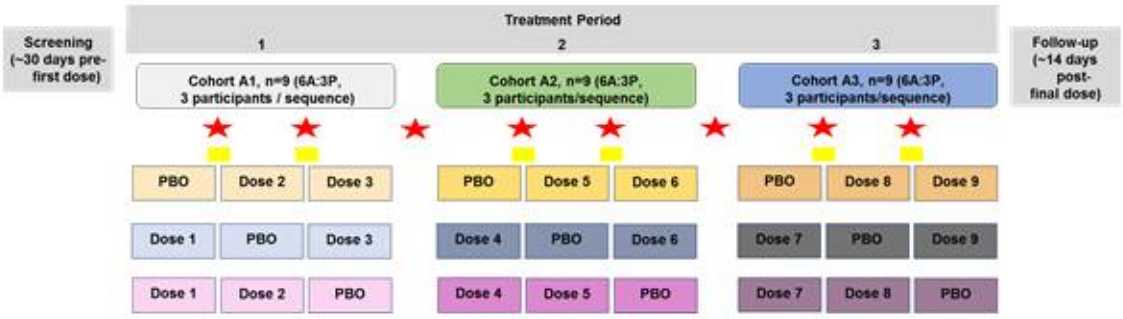
were enrolled in Parts A or B. Participants recruited into Part C will spend approximately 8 weeks enrolled in the study (approximately 30 days screening, approximately 5 day in-house assessment period, and an approximately 14 day follow-up period.

Data Monitoring Committee: Dose Escalation Committee

1.2. Schema

Part A: Single Ascending Dose

Figure 1 Single Ascending Dose Schematic

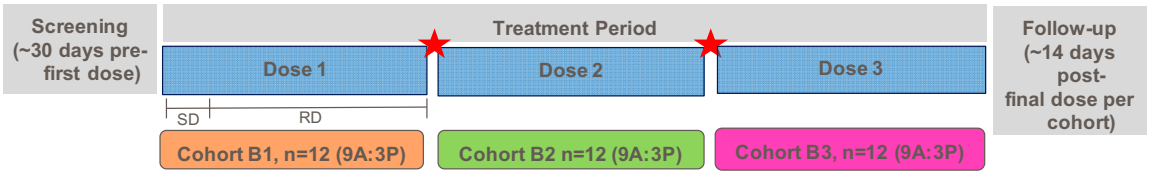


- Within a cohort, participants will be randomized to one of 3 treatment sequences such that each participant receives 2 active doses and 1 placebo dose resulting in each active dose being administered to 6 participants and placebo to 3 participants
- Starting dose (Dose 1) = 5 mg
- Subsequent dose escalations will be determined based on safety and PK data
- Maximum predicted dose = 500 mg (Genotoxic Risk Assessment Limit= 3000mg)
- Washout= 7 days or 5 half-lives, whichever is longer

* = Dose escalation meeting
PBO= Placebo
*Note: dosing strategy is for illustrative purposes and does not represent the randomization strategy

Part B: Single and Repeat Dose 7 or 14-day dose-rising

Figure 2 Repeat Dose Schematic (Part B)

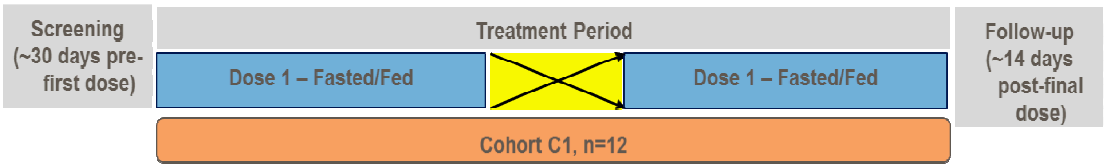


Doses will be selected based on safety, tolerability and PK data from Part A

* = Dose escalation meeting

Part C: Food Effect

Figure 3 Food Effect Schematic (Part C)



- 7-day or 5 half-lives (whichever is longer) washout period/ participant crossover to fasted/fed arm

1.3. Schedule of Activities (SoA)

	Part A- Single Dose									
Procedure	Screening (up to 30 days before Day 1)	Treatment Period [Days] (for each dosing period)						E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	-1	1	2	3	4			
Informed consent	X									
Inclusion and exclusion criteria (including drug screens)	X			X						Recheck clinical status before randomization and/or 1st dose of study medication.
Demography	X									
Physical examination including height and weight	F	B					B	(B)	F	F: Full exam; B: Brief Exam; height is only taken once at screening
Medical history (includes substance usage and family history of premature cardiovascular (CV) disease and any changes in health status occurring between screening and admission to the unit)	X	X								Substances: Drugs, Alcohol, tobacco, and caffeine
Past and current medical conditions	X	X								

	Part A- Single Dose									
Procedure	Screening (up to 30 days before Day 1)	Treatment Period [Days] (for each dosing period)						E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	-1	1	2	3	4			
Human Immunodeficiency Virus (HIV), Hepatitis B and C screening	X									If test otherwise performed within 3 months prior to first dose of study intervention, testing at screening is not required
Admission to Clinical Unit		X								
Safety Laboratory assessments (include liver chemistries)	X	X		X	X	X	X	(X)	X	Predose; 8 hr, 24 hr, and, 48 hr, and 72 hr post-dose and at follow-up visit
Routine Urinalysis	X			X	X	X	X	(X)	X	Predose; 8 hr, 24 hr, 48 hr, and 72 hr post-dose and at follow-up visit
12-lead Electrocardiogram (ECG)	X	X		←==========X==========→				(X)	X	ECGs assessed at screening (triplicate) and admission (single). During treatment period ECGs assessed predose (triplicate at least 5 minutes (min) intervals) and single measurements postdose every 30 min for 1 hr, hourly up to 6 hr, and at 12 hr, 24 hr, 36 hr and 48 hr and 72 hr post-dose

	Part A- Single Dose									
Procedure	Screening (up to 30 days before Day 1)	Treatment Period [Days] (for each dosing period)						E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	-1	1	2	3	4			
Vital signs (pulse rate, blood pressure (bp), respiratory rate, and oral temperature)	X	X		←==========X==========→				(X)	X	Vitals assessed at screening (triplicate measurements for pulse and (bp)) (and admission (single measurements). During treatment period vitals assessed predose (triplicate measurements for pulse and bp) and postdose (single measurements) every 15 min for 1 hr, hourly up to 6 hr, then at 12 hr, 24 hr, 36 hr, 48 hr, and 72 hr post-dose. See Section 8.2.2 for further information
Randomization				X						Randomization will occur before first dose in period 1.
Genetic sample				X						Any time predose on Day 1. This research may be described in a separate Informed Consent Form (ICF) or as part of a combined ICF. A separate signature is required where participant participation is optional
Study intervention				X						

	Part A- Single Dose									
Procedure	Screening (up to 30 days before Day 1)	Treatment Period [Days] (for each dosing period)						E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	-1	1	2	3	4			
Telemetry				X						Telemetry performed starting 30 min (±10 min) pre-dose to 12 hr (±20 min) post-dose
Adverse Event (AE) review				←==========X==========→				(X)	X	
Serious Adverse Event (SAE) review	X	←==========X==========→						(X)	X	
Concomitant medication review	X	←==========X==========→						(X)	X	
24hr urine sampling for Pharmacodynamics (PD)			X[1]	X[2]	X[3]	X[3]		(X)		[1]combined void for windows of 24-22 hr, 22-20 hr, 20-18 hr, 18-16 hr, 16-12 hr, and 12-0 hr predose. [2] combined void for windows of 0-2 hr, 2-4 hr, 4-6 hr, 6-8 hr 8-12 hr, and 12-24 hr post-dose [3]combined void for 24 hr

	Part A- Single Dose									
Procedure	Screening (up to 30 days before Day 1)	Treatment Period [Days] (for each dosing period)						E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	-1	1	2	3	4			
Blood sampling for Pharmacokinetics (PK)				←==========X==========→				(X)		Predose, 5min, 30min, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, and 48 hr, 60 hr, and 72 hr post-dose
24 hr Holter Monitoring				X						Predose through 24 hr post-dose
Discharge from Clinical Unit							X	(X)		

- The timing and number of planned study assessments, including safety, PK, PD/biomarker or other assessments may be altered during the course of 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 ICF. The changes will be approved by the CA and the EC before implementation.

Part B – Repeat Dose																					
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																	E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20			
Informed consent	X																				
Inclusion and exclusion criteria (including drug screens)	X	X																			Recheck clinical status before randomization and prior to muscle biopsy/or 1st dose of study medication.
Demography	X																				
Full physical examination including height and weight	F	B																B	(B)	F	F: Full exam; B: Brief exam; height is only taken once at screening
Medical history (includes substance usage and family history of premature CV disease and any changes in health status occurring between screening and admission to the unit)	X	X																			Substances: Drugs, Alcohol, tobacco, and caffeine
Past and current medical conditions	X	X																			

Part B – Repeat Dose

Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																	E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20			
HIV, Hepatitis B and C screening	X																				If test otherwise performed within 3 months prior to first dose of study intervention, testing at screening is not required
Admission to Clinical Unit		X																			
Safety Laboratory assessments (include liver chemistries)	X	X		X				X[1]		X[1]					X[1]			X	(X)	X[1]	Pre-randomization assessments for eligibility must be performed PRIOR to predose muscle biopsy Predose, 24 hr, and 48, and 72 hr post-Day 1 dose; additional timepoints may be added based on findings in Part A [1]Days 7, 11, 17, 20, and follow-up
Routine urinalysis	X	X		X				X[2]		X[2]					X[2]			X[2]	(X)	X[2]	Predose, 24 hr, 48 hr, and 72 hr post-Day 1 dose; additional timepoints may be added based on findings in Part A [2]Days 7, 11,17, 20, and follow-up

Part B – Repeat Dose																				
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																	E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20			
Hormone monitoring			X												X				(X)		Samples to be taken at midnight and 9am (±10 min) on Days -1 and 17 Samples taken at midnight will be analysed for adrenocorticotropic hormone (ACTH) and cortisol Samples taken at 9am will be analysed for ACTH, cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), total testosterone, dihydrotestosterone (DHT), triiodothyronine (T3), and free thyroxine (free T4) See Section 8.2.7 for information regarding monitoring of abnormal hormone results

Part B – Repeat Dose																				
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20		
12-lead ECG	X	X		←=====X[5]=====→				X[5]		X[5]			X[5]		X[5]			X[5]	(X)	X	ECGs assessed at screening (triplicate measure) and admission (single measure). During treatment period ECGs assessed predose (triplicate measure at at least 5 min intervals) and post-dose (single measure) every 30 min for 1 hr, hourly up to 6 hr, at 12 hr post-dose then at 24 hr, 36 hr, 48 hr, and 72 hr post-dose [5] Days 7,11, 15, and 17, and 20 Post-dose at Cmax based on observed Cmax in Part A (currently estimated to occur at ~2 hr post dose), except for Day 20. Day 20 ECG to occur any time before Discharge

Part B – Repeat Dose

Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20		
Vital signs (pulse rate, bp, respiratory rate, and oral temperature)	X	X		X[6]				X[7]							X[6]				(X)	X	[6]Vitals assessed at screening (triplicate measurements for pulse and bp) and admission (single measurements). During treatment period vitals assessed predose (triplicate measurements for pulse and bp) and postdose (single measurements) every 15 min for 1 hr, hourly up to 6 hr, and at 12 hr, 24 hr, 36 hr, 48 hr, and 72 hr post-dose [7]Vitals assessed once every 24 hr See Section 8.2.2 for further information
Randomization				X																

Part B – Repeat Dose																				
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																	E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20			
Genetic sample				X																	Any time predose on Day 1 This research may be described in a separate ICF or as part of a combined ICF. A separate signature is required where participant participation is optional
Study intervention				X			←==========X==========→														
Telemetry				X																	Telemetry performed starting 30 (±10 min) pre-dose to 12 hr (±20 min) post-dose
AE review							←==========X==========→														
SAE review				←==========X==========→																	
Concomitant medication review				←==========X==========→																	

Part B – Repeat Dose

Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																	E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20			
Urine sampling PD			X[8]	X[9]	X[9]					X[9, 10]					X[9]				(X)		[8]combined void for windows of 24-22 hr, 22-20 hr, 20-18 hr, 18-16 hr, 16-12 hr, and 12-0 hr predose. [9]combined void for windows of 0-2 hr, 2-4 hr, 4-6 hr, 6-8 hr, 8-12 hr, and 12-24 hr post-dose [10] Day 10 only Aliquots will be removed prior to pooling for urine PK. Total urine volume will be recorded before aliquots for PD are removed.

Part B – Repeat Dose																				
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																	E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20			
24h urine sampling for PK and metabolite profiling			X	X	X										X				(X)		Voids from urine pharmacodynamic (PD) sampling windows will be combined into 0-24 hr pools on Day -1,1, and 17 after aliquoting for PD. These voids will be combined for PK/metabolite analysis only after aliquots for urine PD are removed See study reference manual (SRM) for details on samples and processing

Part B – Repeat Dose

Procedure	Screening (up to 30 days before Day 1)			Intervention Period [Days] (for each dosing cohort)														E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20		
Blood sampling for PK				X[11]				X[12]		X[12]			X[12]		X[11]				(X)		[11]Day 1 and Day 17: Predose, 5 min, 30 min, 1 hr, 1. 5hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, 48 hr, 60 hr, and 72 hr post-dose [12]pre-dose samples collected on days 6,7, 9-11 and 15-16
Blood sampling for metabolite profiling				X											X						Day 1 and Day 17: Predose, 5 min, 30 min, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, 48 hr, 60 hr, and 72 hr post-dose
Blood sampling for Pharmacodynamics and biomarkers				X[13]	X[13]					X[14]					X[14]				(X)		[13]Predose and 24 hr post-dose on Day 1 [14]Predose Days 10 and 17

Part B – Repeat Dose

Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																	E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20			
Muscle Biopsy			X[15]												X[16]				(X)		Muscle biopsies must be performed AFTER clinical safety assessments on the corresponding days [15]Day -1 muscle biopsy to occur 1-6 hr after estimated timing of initial dose on Day 1. Time of sample collection to be recorded [16] Day 17 muscle biopsy to occur within 1-6 hr after last dose administered Time of sample collection to be recorded. Muscle biopsy can be performed at any time during pre-dose period.

Part B – Repeat Dose																				
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)																E.D	Follow-up (~14± 1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5-7	8	9-11	12	13-14	15	16	17	18	19	20			
Enterotest (bile sample collection)															X					For second or third dose-level only (depending on PK results in Part A) Enterotest capsule to be swallowed ~2 hr after dosing and removed ~7 hr after dosing (~1 hr after food cue)
Enterotest food cue															X					For second or third dose-level only (depending on PK results in Part A) Food cue will be given 6 hr post-dose
Discharge from Clinical Unit																		X	(X)	

- The time to start the second dose in Part B can be modified based on the estimates of half-life from Part A.
- Duration of dosing in Part B can be modified based on the estimates of half-life from Part A.

- The timing and number of planned study assessments, including safety, PK, PD/biomarker or other assessments may be altered during the course of 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 CA and 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 ICF. The changes will be approved by the CA and the EC before implementation.

Part B .2– 7 Day Repeat Dose																			
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)															E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
Informed consent	X																		
Inclusion and exclusion criteria (including drug screens)	X	X																	Recheck clinical status before randomization and prior to muscle biopsy/or 1st dose of study medication.
Demography	X																		
Full physical examination including height and weight	F	B														B	(B)	F	F: Full exam; B: Brief exam; height is only taken once at screening
Medical history (includes substance usage and family history of premature CV disease and any changes in health status occurring between screening and admission to the unit)	X	X																	Substances: Drugs, Alcohol, tobacco, and caffeine
Past and current medical conditions	X	X																	

Part B .2– 7 Day Repeat Dose																			
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)															E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
HIV, Hepatitis B and C screening	X																		If test otherwise performed within 3 months prior to first dose of study intervention, testing at screening is not required
Admission to Clinical Unit		X																	
Safety Laboratory assessments (include liver chemistries)	X	X		X						X[1]			X[1]			X[1]	(X)	X[1]	Pre-randomization assessments for eligibility must be performed PRIOR to predose muscle biopsy Predose, 24 hr, and 48, and 72 hr post-Day 1 dose; additional timepoints may be added based on findings in Part A [1]Days 7, 10, 13, and follow-up
Routine urinalysis	X	X		X						X[2]			X[2]			X[2]	(X)	X[2]	Predose, 24 hr, 48 hr, and 72 hr post-Day 1 dose; additional timepoints may be added based on findings in Part A [2]Days 7, 10, 13, and follow-up

Part B .2– 7 Day Repeat Dose

Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)														E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13		
Hormone monitoring			X										X					Samples to be taken at midnight and 9am (±10 min) on Days -1 and 10 Samples taken at midnight will be analysed for adrenocorticotropic hormone (ACTH) and cortisol Samples taken at 9am will be analysed for ACTH, cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), total testosterone, dihydrotestosterone (DHT), triiodothyronine (T3), and free thyroxine (free T4) See Section 8.2.7 for information regarding monitoring of abnormal hormone results

Part B .2– 7 Day Repeat Dose																		
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)														E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
12-lead ECG	X	X		←=====X=====→						X[5]			X[5]			X[5]	(X)	X[5]	ECGs assessed at screening (triplicate measure) and admission (single measure). During treatment period ECGs assessed predose (triplicate measure at at least 5 min intervals) and post-dose (single measure) every 30 min for 1 hr, hourly up to 6 hr, at 12 hr post-dose then at 24 hr, 36 hr, 48 hr, and 72 hr post-dose [5] Days 7,10, 13, and Follow-up Post-dose at Cmax based on observed Cmax in Part A (currently estimated to occur at ~2 hr post dose), except for Day 13 . Day 13 ECG to occur any time before Discharge

Part B .2– 7 Day Repeat Dose

Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)															E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
Vital signs (pulse rate, bp, respiratory rate, and oral temperature)	X	X		X[6]				X[7]								X[6]	(X)	X	[6]Vitals assessed at screening (triplicate measurements for pulse and bp) and admission (single measurements). During treatment period vitals assessed predose (triplicate measurements for pulse and bp) and postdose (single measurements) every 15 min for 1 hr, hourly up to 6 hr, and at 12 hr, 24 hr, 36 hr, 48 hr, and 72 hr post-dose [7]Vitals assessed once every 24 hr See Section 8.2.2 for further information
Randomization				X															
Genetic sample				X															Any time predose on Day 1 This research may be described in a separate ICF or as part of a combined ICF. A separate signature is required where participant participation is optional

Part B .2– 7 Day Repeat Dose																		
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)														E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
Study intervention				X			←==========X==========→											
Telemetry				X														Telemetry performed starting 30 (±10 min) pre-dose to 12 hr (±20 min) post-dose
AE review		←==========X==========→																
SAE review	←==========X==========→																	
Concomitant medication review	←==========X==========→																	

Part B .2– 7 Day Repeat Dose																		
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)														E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
Urine sampling PD			X[8]	X[9]						X[9]			X[9]				(X)		[8]combined void for windows of 24-22 hr, 22-20 hr, 20-18 hr, 18-16 hr, 16-12 hr, and 12-0 hr predose. [9]combined void for windows of 0-2 hr, 2-4 hr, 4-6 hr, 6-8 hr, 8-12 hr, and 12-24 hr post-dose Aliquots will be removed prior to pooling for urine PK. Total urine volume will be recorded before aliquots for PD are removed.

Part B .2– 7 Day Repeat Dose

Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)															E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
24h urine sampling for PK and metabolite profiling			X	X									X				(X)		Voids from urine pharmacodynamic (PD) sampling windows will be combined into 0-24 hr pools on Day -1,1, and 10 after aliquoting for PD. These voids will be combined for PK/metabolite analysis only after aliquots for urine PD are removed See study reference manual (SRM) for details on samples and processing
Blood sampling for PK				X[10]					X[11]	X[11]		X[11]	X[10]				(X)		[10]Day 1 and Day 10: Predose, 5 min, 30 min, 1 hr, 1. 5hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, 48 hr, 60 hr, and 72 hr post-dose [11]pre-dose samples collected on days 6, 7, and 9

Part B .2– 7 Day Repeat Dose																		
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)														E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
Blood sampling for metabolite profiling				X									X						Day 1 and Day 10 Predose, 5 min, 30 min, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, 48 hr, 60 hr, and 72 hr post-dose
Blood sampling for Pharmacodynamics and biomarkers				X[12]	X[12]					X[13]			X[13]				(X)		[12]Predose and 24 hr post-dose on Day 1 [13]Predose Days 7 and 10

Part B .2– 7 Day Repeat Dose																		
Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days] (for each dosing cohort)														E.D	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–2	–1	1	2	3	4	5	6	7	8	9	10	11	12	13			
Muscle Biopsy			X[14]										X[15]				(X)		Muscle biopsies must be performed AFTER clinical safety assessments on the corresponding days [14]Day -1 muscle biopsy to occur 1-6 hr after estimated timing of initial dose on Day 1. Time of sample collection to be recorded [15]Day 10 muscle biopsy to occur within 1-6 hr after last dose administered Time of sample collection to be recorded. Muscle biopsy can be performed at any time during pre-dose period.
Discharge from Clinical Unit																X	(X)		

- The time to start the second dose in Part B can be modified based on the estimates of half-life from Part A.
- Duration of dosing in Part B can be modified based on the estimates of half-life from Part A.
- The timing and number of planned study assessments, including safety, PK, PD/biomarker or other assessments may be altered during the course of 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 CA and 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 ICF. The changes will be approved by the CA and the EC before implementation.

Part C- Food Effect									
	Screening (up to 30 days before Day 1)	Treatment Period [Days] (with or without food)					E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–1	1	2	3	4			
Informed consent	X								
Inclusion and exclusion criteria (including drug screens)	X		X						Recheck clinical status before randomization and/or 1st dose of study medication.
Demography	X								
Physical examination including height and weight	F	B				B	(B)	F	F: Full exam; B: Brief Exam; height is only taken once at screening

Part C- Food Effect									
	Screening (up to 30 days before Day 1)	Treatment Period [Days] (with or without food)					E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–1	1	2	3	4			
Medical history (includes substance usage and family history of premature CV disease and any changes in health status occurring between screening and admission to the unit)	X	X							Substances: Drugs, Alcohol, tobacco, and caffeine
Past and current medical conditions	X	X							
HIV, Hepatitis B and C screening	X								If test otherwise performed within 3 months prior to first dose of study intervention, testing at screening is not required
Admission to Clinical Unit		X							

Part C- Food Effect									
	Screening (up to 30 days before Day 1)	Treatment Period [Days] (with or without food)					E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–1	1	2	3	4			
Safety Laboratory assessments (including liver chemistries)	X	X	X	X	X	X	(X)	X	Predose; 8 hr, 24 hr, 48 hr, and 72 hr post-dose and at follow-up visit
Routine Urinalysis	X		X	X	X	X	(X)	X	Predose; 8 hr, 24 hr, 48 hr, and 72hr post-dose and at follow-up visit
12-lead ECG	X	X	←==========X==========→				(X)	X	ECGs assessed at screening (triplicate) and admission (single). During treatment period ECGs assessed predose (triplicate at least 5 min intervals) and single measurements postdose every 30 min for 1 hr, hourly up to 6 hr, and at 12 hr, 24 hr, 36 hr, 48 hr, and 72 hr post-dose

Part C- Food Effect									
	Screening (up to 30 days before Day 1)	Treatment Period [Days] (with or without food)					E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–1	1	2	3	4			
Vital signs (pulse rate, bp, respiratory rate, and oral temperature)	X	X	←==========X==========→				(X)	X	Vitals assessed at screening (triplicate measurements for pulse and bp) and admission (single measurements). During treatment period vitals assessed predose (triplicate measurements for pulse and bp) and postdose (single measurements) every 15 min for 1 hr, hourly up to 6 hr, and at 12 hr, 24 hr, 36 hr, 48 hr, and 72 hr post-dose See Section 8.2.2 for further information
Randomization			X						
Genetic sample			X						Sample can be obtained at any point during dosing. This research may be described in a separate ICF or as part of a combined ICF. A separate signature is required where participant participation is optional

Part C- Food Effect

	Screening (up to 30 days before Day 1)	Treatment Period [Days] (with or without food)					E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–1	1	2	3	4			
Test Meal			X						Fed Arm only. See Section 5.3.1 for timings regarding meals, fasting, and treatment administration
Study intervention			X						
Telemetry			X						Telemetry performed starting 30 min (±10 min) pre-dose to 12hrs (±20 min) post-dose
AE review			←==========X==========→				(X)	X	
SAE review	X	←==========X==========→						(X)	
Concomitant medication review	X	←==========X==========→					(X)	X	
Blood sampling for PK			←==========X==========→				(X)		Predose, 5 min, 30 min, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, and 48 hr, 60 hr, and 72 hr post-dose

Part C- Food Effect									
	Screening (up to 30 days before Day 1)	Treatment Period [Days] (with or without food)					E.D.	Follow-up (~14±1 days post last dose)	Notes E.D = early discontinuation/withdrawal
		–1	1	2	3	4			
Discharge from Clinical Unit						X	(X)		

- Duration of dosing in Part C can be modified based on the estimates of half-life from Part A.
- The timing and number of planned study assessments, including safety, PK, PD/biomarker or other assessments may be altered during the course of 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 CA and 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 ICF. The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

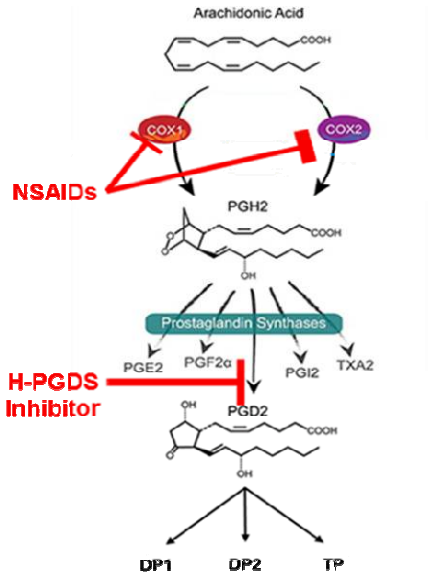
2.1. Study Rationale

This study is the first time into human study (FTIH) for GSK3439171A. The study will evaluate the safety, tolerability and pharmacokinetics (PK) of single ascending and repeat oral doses of GSK3439171A in healthy adult participants. A food effect assessment will be undertaken using a crossover design to investigate the influence of food on the PK of GSK3439171A. Pharmacodynamic (PD) and biomarker effects of GSK3439171A in healthy adult volunteers will also be explored. The results of this study are intended to be used to identify appropriate and well tolerated oral doses to be used in further studies investigating GSK3439171A in diseases in which prostaglandin-mediated pathways are involved.

2.2. Background

2.2.1. Hematopoietic prostaglandin D2 synthase (H-PGDS)

Figure 4 Prostanoid Synthesis



Schematic of prostanoid synthesis via the arachidonic acid cascade, modified from Figueiredo-Pereira (2015)

Prostaglandin D_2 (PGD_2) is a downstream product of the arachidonic acid cascade (Figure 4) and is synthesized by mast cells in response to stimulation via multiple injurious mechanisms and cellular activation pathways [Lewis, 1982]. Other cells such as dendritic cells, T helper 2 (Th2) cells, and epithelial cells also produce PGD_2, but at lower levels than mast cells. PGD_2 mediates its effects via activation of the specific G-protein coupled receptors DP1 [Boie, 1995] and DP2 (CRTH2) [Abe, 1999] and also acts via the receptor for thromboxane A2 (TXA_2), the TP receptor, on target cells [Hirata, 2011].

The cyclo-oxygenase (COX) enzymes convert arachidonic acid in a two-step process, first to PGG_2 and then to the unstable endoperoxide, PGH_2. The PGD synthase (PGDS) enzyme is subsequently responsible for the catalytic isomerization of PGH_2 to PGD_2 [Smith, 2011]. PGD_2 is generated by the action of either H-PGDS (hematopoietic-type or H-type) or L-PGDS (lipocalin-type or L-type) enzymes [Urade, 2000]). PGDS is the key regulator of PGD_2 synthesis by mast cells and antigen-presenting cells of the immune system, and orchestrates mechanisms of inflammation in muscle disorders (acute injury and chronic degenerative diseases), allergy and asthma. Strong biological evidence demonstrates H-PGDS-mediated PGD_2 production impairs skeletal muscle repair [Mohri, 2009], and blockade of this signal via gene manipulation, using knock-out (KO) mice, and small molecule inhibition of either H-PGDS or the PGD_2 receptors DP1 and DP2 accelerates the kinetics of muscle remodeling and functional recovery. Additionally, tissue levels of H-PGDS and PGD_2 are elevated in acutely injured tissue and chronically inflamed tissue. Notably, H-PGDS inhibitors increase markers of myogenesis (MyoD and myogenin) following muscle injury in animals. Taken together, selective inhibition of H-PGDS offers potential to improve muscle adaptation, aiding recovery from injury, for example during rehabilitation.

Importantly, other products of arachidonic acid metabolism such as PGE_2 and PGF2α produce beneficial signaling in muscle [Korotkova, 2014] and therefore approaches that decrease global inflammatory signaling (e.g. nonsteroidal anti-inflammatory drugs, NSAIDs) are not efficacious. This may be especially pertinent to populations recovering from surgical interventions involving tendons and associated structures, where NSAIDs can block tendon healing [Cohen, 2006; Connizzo, 2014].

2.2.2. GSK3439171A

GSK3439171A is a potent, reversible, and highly selective azetidine urea inhibitor of H-PGDS – the major enzyme responsible for the production of PGD2 in mast cells. All information regarding non-clinical safety and pharmacology is available in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2018N359817_00]. GSK3439171A has not been previously administered to human participants; therefore, there are no clinical data available.

This first clinical study, which will constitute the initial administration to humans, will be conducted in healthy human participants.

2.3. Benefit/Risk Assessment

Consistent with GlaxoSmithKline (GSK) guidance for early phase studies, GSK3439171A will be administered in an in-patient setting (with sufficient overnight facilities) in the United States with appropriate monitoring.

In order to minimise the risk of the initial human administration of GSK3439171A, a sentinel dosing strategy will be utilized in each of the cohorts in Part A: 1 participant will receive GSK3439171A and 1 participant will receive placebo. After the GSK medical monitor and investigator have reviewed the safety data through 48 hrs post-dose, (or 5 half-lives, whichever is longer) the remaining participants from that cohort will be dosed.

Once all assessments through 48 hours post-dose (or 5 half-lives, whichever is longer) have been completed for a minimum of 4 participants on active treatment at each dose level, the GSK team and the investigator will review all of the available safety and PK data from all participants before proceeding to the next dose level.

Summaries of findings from non-clinical studies conducted with GSK3439171A can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK3439171A]		
Potential effect on liver	In adult dogs at oral doses levels up to 600 mg/kg/day for 6 weeks, GSK3439171 was associated with minimal to slight changes in the liver (mixed periportal inflammatory cell infiltrates at ≥100 mg/kg/day) that generally correlated with increases in serum ALT, glutamate dehydrogenase (GLDH) and/or alkaline phosphatase (ALKP). Mean serum levels were increased for ALT: 2.4 to 4.7 times, for GLDH: 2.6 to 4 times, and for ALKP: 1.1 to 2.2 times Baseline values. Findings were dose and exposure-responsive with respect to magnitude, severity and incidence. The dog liver finding is considered monitorable in clinical setting and not dose limiting. The high dose of 600 mg/kg/day was associated with systemic exposure AUC (0-t) of 57.8 µg.h/mL in male dogs.	The stopping exposure limits for the single dose phase were set by the dog liver toxicity and the following liver chemistry criteria are in place: Elevation of alanine aminotransferase (ALT) and other liver tests (aspartate aminotransferase [AST], bilirubin [total and direct])
Potential effect on endocrine system (adrenal gland)	In juvenile rats, recoverable, dose responsive findings were noted in the adrenal gland (cortical hypertrophy of the zona fasciculata) with associated increased adrenal weights, pale discoloration and/or enlargement in males given ≥100 mg/kg/day and females given ≥10 mg/kg/day. As the findings may be considered potentially adverse for repeat clinical dosing, the no adverse effect level (NOEL) for adrenal gland histologic	The AUC stopping exposure limit of 11 µg.hr/mL for the repeat dose phase is below (0.24 times) the lowest effect exposure for rat adrenal toxicity and participants will be monitored at times indicated in the SoA for changes in the following levels:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	effects was 10 mg/kg/day in male and female rats, with associated AUC (0-t) of 3.94 µg.h/mL. The lowest individual AUC at lowest effected dose level (LOEL) of 100 mg/kg/day for male juvenile rat adrenal effects is 46 µg.h/mL.	adrenocorticotropic hormone (ACTH), cortisol luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH) total testosterone dihydrotestosterone (DHT) thyroxine (T4) triiodothyronine (T3)
Potential effect on female reproductive tissues	In female juvenile rats, recoverable, dose responsive microscopic findings were also noted in the ovary (vacuolation of interstitial cells) and mammary gland (lobuloalveolar hypertrophy/hyperplasia) at ≥100 mg/kg/day; and pituitary (increased mitoses of cells in the pars distalis) at 600 mg/kg/day.	All women will be excluded from this study.
The nonclinical toxicology and efficacy studies were conducted using non-micronized material, while	The rat and dog toxicity studies with non-micronized material attained AUC and Cmax exposures substantially over the NOAEL to effectively characterize the nonclinical safety of GSK3439171. Additionally, the	Conservative assumptions were used for the minimum anticipated biological effect level (MABEL) simulations and the predictions for the first dose are expected to be well

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
this clinical study will use micronized, thus there is a risk that the clinical PK will be different than predicted	impurity profile of the micronized material was consistent with that of the non-micronized material. Thus, the nonclinical safety data is considered supportive of clinical use of micronized compound.	below the dog NOAEL exposure margins, 110- and 270-fold lower for AUC(0-inf) and Cmax, respectively. The suspension used for non-clinical studies was homogenised and the particle size thus reduced smaller than non-micronised. Solubility does not change on micronisation but in-vitro bio-relevant dissolution data shows a proportional response in rate of dissolution for non-micronised, ground and micronized.
Study Procedures		
Entero-Test Streaks of blood on the string due to local irritation have been infrequently noted. Rarely, a patient will be unable to swallow the capsule because of gagging or will vomit after doing so. Gagging upon retrieval of the string can occur. On a few occasions, an entire string has been swallowed without ill effects		The use of Entero-Test has been approved by the FDA (510(k), Summary of safety and effectiveness). The string will be securely taped in place during the collection time to minimize risk of swallowing the entire string. Any subject incapable of swallowing the capsule will be allowed to participate in the study without duodenal bile collection.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
and passes from the body in the feces. Consider risks associated with comparators, challenge agents, imaging agents, medical devices, etc		
Muscle Biopsy Localized pain from muscle biopsy procedure can occur Low risk of bleeding or infection could occur as result of the procedure. There is a very low risk of nerve damage as a result of the procedure		Local anesthetic will be employed during muscle biopsy procedures. Acetaminophen or another medication selected by the investigator and the medical monitor can be administered to participants to control post-procedural pain. Biopsy procedure will be performed by staff experienced in the technique. Participants will be followed up for any adverse events resulting from the biopsy and managed appropriately, if needed.

2.3.2. Benefit Assessment

There will be no benefit to the participant taking part in this study. However, participants will be contributing to the process of developing new therapies by taking part in the study.

2.3.3. Overall Benefit: Risk Conclusion

The measures taken to minimize the potential risks identified in association with GSK3439171A are considered sufficient to justify participation by healthy participants.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of GSK3439171A following single and repeat doses in healthy participants	• Adverse events (AE), clinical laboratory values, vital signs, and electrocardiograms (ECG)
• To characterize the PK of GSK3439171A, following single and repeat doses in healthy participants	• Derived PK parameters for GSK3439171A including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-inf), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and apparent terminal half-life ($t_{1/2}$) as appropriate
Secondary	
• To assess the effect of food on the PK of GSK3439171A following an oral dose in healthy participants	• Derived PK parameters for GSK3439171A including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-inf), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), and apparent terminal half-life ($t_{1/2}$) as appropriate
• To assess preliminary dose proportionality of GSK3439171A	• AUC(0-t), AUC(0-inf), and Cmax following single dose and AUC(0-τ)

Objectives	Endpoints
following single and repeat oral doses, as data permit	and Cmax following repeat dose for the assessment of dose proportionality
• To examine the extent of accumulation and achievement of steady-state following repeat oral doses of GSK3439171A, as data permits	• Determine observed accumulation based on AUC(Ro) and Cmax (RCmax) and determine the steady-state ratio (Rss) • Trough plasma concentrations at the end of the dosing interval (C_τ) collected pre-dose for repeat doses 3, 4, 12, 13 and 14 (repeat doses 3,4,6, and 7 for 7 day dosing) to assess the achievement of steady-state of GSK3439171A
Exploratory • To evaluate the PD properties of GSK3439171A	• Levels of mediators on prostaglandin and/or inflammatory metabolic pathways such as, but not limited to, PGD2, and PGE2.
• To assess the effect of GSK3439171A on QTc in healthy adult volunteers	• Holter monitor data collection and storage for evaluation of the correlation between plasma levels of GSK3439171A and changes in the QTc interval in the future, if appropriate
• To evaluate additional biomarkers of GSK3439171A target engagement after single and repeat doses.	• Levels of change in novel biomarkers in blood, muscle, or urine, such as, but not limited to, urine tetranor PGDM and PGEM (tPGDM, tPGEM), PGD2, and PGE2
• To investigate the plasma, urinary and biliary (Part B) metabolic pathways of GSK3439171A in healthy subjects	• GSK3439171A-related material in plasma, urine and bile.

4. STUDY DESIGN

4.1. Overall Design

This is a three-part study (Parts A, B and C). Part A will be a double-blind (sponsor unblinded), single oral dose, dose-rising, placebo-controlled, randomized (with respect to placebo allocation), 3 period crossover study in approximately 3 cohorts of participants. Part B will be double-blind (sponsor unblinded), up to 14 day repeat oral dosing, placebo-controlled, randomized (with respect to placebo allocation), dose escalation study with at least three dose levels in 3 separate cohorts of participants who were not enrolled into Parts A or C of this study. Part C will be an unblinded, randomized, crossover study where a single dose will be administered fasted or fed conducted in a separate cohort of participants than those who were enrolled in Parts A or B.

The starting dose for Part A will be 5 mg (see Section 4.3.3).

Part A: Single Ascending Dose

Each participant will participate in 3 dosing periods and will receive 2 doses of GSK3439171A and 1 dose of placebo in a randomized fashion. There will be an approximately 7 day (or 5 half-lives, whichever is longer) washout period between dosing in each session.

Approximately 9 participants will be enrolled in each cohort. Participants will be admitted to the clinical unit on Day -2 and will remain in the unit until completion of assessments on Day 4 as outlined in the SoA. Participants will be discharged from clinical unit for the washout period between dosing sessions and will return approximately 14 days after dosing in their last dosing session for a follow-up visit. Participants will be randomized to treatment sequences such that in each period up to 6 participants will receive active dose and up to 3 participants will receive placebo. A minimum of three cohorts is anticipated. If a participant is withdrawn from the study, the participant may be replaced as necessary with another participant assigned to the same treatment sequence with respect to active and placebo doses to ensure that at least 4 participants receive each active dose and 1 participant receives a placebo, and that these participants complete safety and PK assessments through at least 72hr post-dose (or 5 half-lives, whichever is longer). Additional participants may be dosed at a given level if additional data are necessary to establish safety, tolerability or PK parameters prior to dose escalation.

Each active dose level will be administered initially to a smaller group of participants (1 on active and 1 on placebo) to evaluate safety at each dose level. These sentinel participants will be followed clinically for 48 hr (or 5 half-lives, whichever is longer) to allow for adequate observation of safety (given a predicted half-life of 6.1 hr for GSK3439171A) after dose administration to monitor for emergence of adverse events. If no acute safety issues are observed in this smaller group of sentinel participants (including review of 48 hr safety laboratory results), then the remaining participants (approximately 5 participants on active and 2 participants on placebo) will receive this

same dose prior to dose escalation. See Section 6.6 for information on the decision to proceed to the next dose level.

Part B: Single and Repeat Dose up to 14-day dose-rising

In each cohort of Part B of the study, approximately twelve participants will be randomized to either one dose level of GSK3439171A or placebo according to a randomization schedule prepared prior to the start of the study. The study will be conducted sequentially starting with Dose 1 Cohort B1. Participants will receive repeat daily or twice daily (BID) doses of the study intervention or placebo based on ongoing PK data obtained in Parts A and B.

Participants will report to the Clinical Research Unit on Day -2 and will remain in the unit for the duration of Part B. Participants will randomly be assigned to receive a single dose (or a BID dose depending on data obtained in Part A) of GSK3439171A or placebo (approximately 9 study intervention: 3 placebo). Plasma and urine PK, PD, and biomarker samples (including a pre-dose muscle biopsy) will be collected for up to 72 hr after initial dosing. After completion of assessments at 72 hr (Day 4), participants will begin a repeat dosing regimen consisting of one dose (or a BID dose depending on data obtained in Part A) per day for up to 14 days. This time period is based on a predicted half-life of GSK3439171A of 6.1 hours (with a range of 4-22 hours) calculated from preclinical data and is designed to allow GSK3439171A to reach steady state during the dosing period. The actual repeat dose duration can be altered based on PK data in Part A of the study. For example, if the predicted half-life is confirmed from Part A of the study then the duration of dosing in Part B will be much shorter to achieve steady-state than planned currently. Dosing duration in Part B and follow-up will be shortened appropriately based on emerging PK data from Part A. Participants will be discharged on the morning of Day 13 (3 days post last dose during the 7 day repeat dose period) or Day 20 (3 days post-last dose during the 14 day repeat dose period) following completion of study assessments, including a post-dose muscle biopsy. Safety, tolerability and PK data review for a minimum of 6 participants receiving active treatment will be carried out upon completion of assessments on Day 13 or 20 (72 hours post-last dose) before initiation of dosing in the next cohort. The dose of GSK3439171A may be adjusted (lower or higher) based on data from Part A and for cohorts going forward based upon the safety, tolerability, PK, and preliminary PD data from the previous cohort.

All participants will return to the clinical unit for a follow-up visit approximately 14 days following the administration of the last dose of study medication.

Part C: Food Effect

In this crossover design, approximately 12 participants will take part in two approximately 4-day study sessions with dosing in each session separated by approximately 7 days (or 5 half-lives of the study intervention, whichever is longer). In each study session, participants will be admitted to the clinical unit and receive a single dose of GSK3439171A either in the fasted state or after a high fat meal. Participants will be randomly assigned to one of two treatment sequences in a two-period crossover design (fed/fasted or fasted/fed). The timing of assessments in Part C can be altered based upon data obtained in Parts A and B.

The dose of GSK3439171A to be administered will be determined from Parts A and B to ensure an adequate safety margin assuming an arbitrary 2-fold increase in exposure to GSK3439171A when administered with food. Participants will remain in the unit for completion of safety and PK assessments before being discharged on Day 4. Participants will return for a follow-up visit approximately 14 days following the administration of the last dose of study medication.

The total duration of the study for each participant recruited into Part A will be approximately 10 weeks. For participants recruited into Part B, the total study duration will be up to approximately 9 weeks. For participants recruited into Part C, the total study duration will be up to approximately 8 weeks.

4.2. Scientific Rationale for Study Design

The FTIH study with GSK3439171A will evaluate the safety of GSK3439171A in healthy participants in order to avoid confounding factors due to the disease or concomitant drugs in patients. The study design is based on pre-clinical findings for GSK3439171A, contributing to the frequency, type and duration of safety assessment and monitoring during treatment periods in each cohort.

The single dose assessments in Part A will be conducted to determine safety, tolerability, PK, and PD of the study intervention in individuals before progressing to doses explored further in other parts of the study. The sequential design of the single dose components will allow for dose escalation to occur approximately every two weeks with a 7-day period of washout. This approach allows for any adjustments needed based on emerging safety, tolerability, and PK information. The crossover design within each cohort in Part A is preferred as it allows for each participant to serve as their own control for the assessment of safety and provides PK assessment in the same individual at two different dose levels, reducing the influence of inter-individual variability.

In Part B, a single dose safety, tolerability and PK will be collected followed by progression of these participants to the repeat dose portion of the study. The 7 or 14-day dosing was chosen as it is thought to provide sufficient safety and tolerability data to bridge to longer duration studies. The dosing period can be adjusted depending on PK and PD data collected in Part A of the study.

Prostaglandin species, particularly prostaglandin D2, are virtually undetectable in the blood or plasma of unchallenged and/or otherwise healthy human subjects. However, skeletal muscle contains high levels of prostanoids in the basal state, and our preclinical data reveal significant dose-dependent reductions in prostaglandin D2 levels in skeletal muscle following administration of H-PGDS inhibitors [GSK3439171A Investigator's Brochure]. Therefore, muscle biopsies will be performed both pre- and post-study intervention in Part B to assess the effect of GSK3439171A on prostanoid levels *in situ* in a tissue of potential clinical interest.

During preclinical pharmacokinetic assessments, GSK3439171A was found to be highly bioavailable (generally >40%); however, recovery of GSK3439171A in urine was low (<2% of the administered dose) [GSK3439171A Investigator's Brochure]. In order to characterize potential biliary elimination pathways, this study will also employ the

Entero-Test for sampling of bile to conduct qualitative assessment of drug metabolites in this matrix. The Entero-Test is an easy-to-use and minimally-invasive method for sampling bile from the duodenum.

Entero-Test is a FDA approved device for human non-invasive sampling of upper gastro-intestinal content. Information on the biliary disposition of drug-related material derived in the current study may avoid the need for invasive methods of bile collection in future studies. As sufficient data from the Entero-Test string is expected following one dose of the study drug, this assessment will be restricted to only one cohort in Part B (anticipated to be the second or third dose level depending on PK results in Part A) at participants' last dose. In addition, urine will be collected and used to investigate the urinary elimination of parent drug and any metabolites alongside bile analysis as well as analysis of PK samples for drug and metabolites (under a separate protocol).
Additionally, Holter monitor data will be collected and stored for a future evaluation of the correlation between plasma levels of GSK3439171A and changes in the QTc interval, if appropriate.

The crossover design for assessing the effect of food on GSK3439171A in Part C allows each participant to serve as their own control, reducing the influence of potential inter-individual variability in this part of the study.

The 7-day (or 5 half-lives, whichever is longer) washout utilized in Parts A and C of the study is believed to provide sufficient washout based on preclinical data and simulations but can be modified based on emerging data in Part A.

4.3. Justification for Dose

Dose selection of GSK3439171A for this FTIH study was based on NOAEL data in the most sensitive species, predicted PK of humans using the PK data from preclinical species, and a target therapeutic exposure based on the in-vitro H-PGDS recombinant enzyme assay, and in-vivo dose-response evaluation of GSK3439171A in wild-type (WT) eccentric damage and dystrophin deficient (mdx) mouse models.

The human PK parameters were calculated from preclinical mouse, rat, dog and monkey data. A range of human clearance and volume of distribution values were estimated by a variety of liver blood flow (LBF), allometric scaling, and Physiologically Based PK (PBPK) methods using GlaxoSmithKline software package PK Predictor Pro version 2.0.2.8, Excel and GastroPlus 9.0, respectively. Human bioavailability was estimated by averaging the oral bioavailability of mice, rat, dogs, and monkeys and estimated from LBF and single species scaling. Based on allometry and LBF, the predicted median human clearance was 10.8 mL/min/kg. The predicted median (range) human volume of distribution was 4.6 L/kg (3.2-6.0) and the predicted median (range) of half-life was 6.1 h (4-22). The human oral absorption rate was assumed to be 6.0 h^{-1}, based upon the average of the preclinical species (7.5 h^{-1}). The predicted oral bioavailability median (range) was 61% (39%-68%). A 100% bioavailability can be used as a conservative approach.

GSK3439171 was given orally to adult dogs for 6 weeks, and rats for 8 weeks starting dosing as juveniles on Postnatal Day (PND) 28 through maturity. Principal toxicities were a slight microscopic liver effect in the dog (inflammatory cell infiltrates in

periportal region) which was associated with elevations in liver enzyme activity, and adrenal gland and female reproductive tissue effects in the juvenile rat. In both species there was a sex difference in systemic exposure, with the females generally having higher exposure. For dogs with liver findings that were associated with increases in alanine aminotransferase activity (ALT), glutamate dehydrogenase (GLDH) or alkaline phosphatase (ALKP) activity, findings were dose and exposure-responsive with respect to magnitude, severity and incidence. Mixed inflammatory cell infiltrates in the liver combined with the increases in liver-related enzymes were considered adverse at ≥100 mg/kg/day; thus, the NOAEL in dogs for 6 weeks duration was considered to be 20 mg/kg/day with females having higher exposure (AUC: 11.0 µg.h/mL). Since the dog liver finding is monitorable in a clinical setting and not considered dose limiting, the male exposure at 600 mg/kg/day (AUC: 57.8 µg.h/mL) is considered acceptable as a clinical single exposure limit for Part A. In juvenile rats, recoverable, dose-responsive findings were noted in the adrenal gland (cortical hypertrophy of the zona fasciculata) with associated increased adrenal weights, pale discoloration and/or enlargement in males given ≥100 mg/kg/day and females given ≥10 mg/kg/day. At 10 mg/kg, 1 of 10 female rats had pale discoloration and an increased adrenal gland weight, without a microscopic change. The rat adrenal findings may be considered potentially adverse, the NOEL for adrenal gland histologic effects was 10 mg/kg/day in male and female rats, with associated AUC (0-t) of 3.94 µg.h/mL. The lowest individual AUC at the lowest effected dose level (LOEL) of 100 mg/kg/day for male juvenile rat adrenal effects is 46 µg.h/mL. In a preliminary study, there were no adrenal macroscopic or microscopic effects in adult male rats after 7 days of dosing 1000 mg/kg/day (AUC in blood: 1130 µg.h/mL).

In female juvenile rats, recoverable, dose responsive microscopic findings were also noted in the ovary (vacuolation of interstitial cells) and mammary gland (lobuloalveolar hypertrophy/hyperplasia) at ≥100 mg/kg/day; and pituitary (increased mitoses of cells in the pars distalis) at 600 mg/kg/day.

Results of other nonclinical studies suggest that GSK3439171 does not present a genotoxic risk to humans. Additionally, there were no safety pharmacology findings of clinical concern at oral dog doses up to 1500 mg/kg. There were no changes considered related to GSK3439171 administration in the evaluation of spermatogenesis in either species. Thus, the nonclinical data support the conduct of clinical studies in men up to 6 weeks duration up to the mean systemic exposure at the NOEL for adrenal gland histologic effects in the rat study (AUC: 3.94 µg.h/mL) with appropriate monitoring in place, and for a shorter duration of 7 days up to the dog liver NOAEL exposure (AUC: 11.0 µg.h/mL).

Based on in vivo efficacy studies and mechanism of the H-PGDS pathway, the efficacy target was to maintain GSK3439171A concentrations above the IC_{50}. A 10% inhibition of the H-PGDS enzyme (IC_{10}) was considered as the minimal anticipated biological effect level (MABEL). The IC_{50} and IC_{10} were calculated from the H-PGDS recombinant enzyme inhibition assay and compared with in vivo studies (dystrophin deficient (mdx) and WT eccentric damage mouse models).

GSK3439171A in vitro inhibition was evaluated using a recombinant human H-PGDS enzyme assay. The data was fitted using an E_{max} model and the IC_{50} was 7.77 ng/mL and

the IC_{10} was 0.86 ng/mL. The target IC_{50} was compared to the in vivo efficacy studies in the WT eccentric damage mouse model and a dystrophin deficient (mdx) mouse model which is a commonly used preclinical model to mimic Duchenne muscular dystrophy. In these models, the corresponding ED_{50} (0.7 mg/kg/day and 0.6 mg/kg/day, respectively) and IC_{50} (5.5 ng/mL and 4.7 ng/mL, respectively) were comparable. Briefly, in these studies, 8-month old male mice were administered an initial dose of vehicle or 0.1, 0.3, 1.0, 3.0, 10 and 30 mg/kg of GSK3439171A 10 minutes prior to a challenge of 60 eccentric contraction repetitions, and then daily (BID, per oral (PO)) administration thereafter for 46 days. On day 45, serial blood samples were collected from a subset of animals (n=3) in each dose group and the steady state pharmacokinetic parameters were estimated. At varying intervals, maximal isometric limb torque was measured *in vivo* to assess functional recovery. Whereas vehicle-treated mdx mice exhibited prolonged recovery kinetics and never fully reached their starting (Baseline) function (~30% permanent force deficit), GSK3439171A-treated animals recovered significantly faster with significantly greater resolution of their force deficit. In the efficacy studies, longitudinal composite of muscle function pre-damage, and intermittently throughout the 46-day study was obtained. GSK3439171A provided a significantly protective effect to the initial insult at doses ≥1 mg/kg. Limb recovery over time was normalized to Baseline from day 0 and was used as an integrated measure of the pharmacological effect to calculate an ED50 of 0.6 mg/kg/day with a 95% confidence interval ranging from 0.14 – 2.8 mg/kg/day. Thus, based on the H-PGDS enzyme inhibition evaluation, the target IC_{50} and IC_{10} values were 7.77 ng/mL and 0.86 ng/mL, respectively.

PK simulations (100 replicates) were performed in a 70-kg human using an estimated median clearance (10.8 mL/min/kg) and volume of distribution (4.6 L/kg) with 30% between-subject variability assuming a 1-compartment model. Based on the results, a 37 mg BID dose would achieve concentrations greater than the target IC_{50} in more than 90% of patients.

4.3.1. Maximum Recommended Starting Dose (MRSD)

Using the FDA Guidance for estimation of the maximum safe starting dose, the NOAEL in female dogs was converted to the Human Equivalent Dose (HED) based on body surface area. After applying an uncertainty safety factor of 10 (guideline default) to the HED, the maximum recommended starting dose for a 60-kg adult is 66.7 mg.

4.3.2. Dose Predicted to Achieve the Therapeutic Exposure Target

The primary in vivo efficacy study was a dose-response evaluation of GSK3439171A on the H-PGDS recombinant enzyme and compared with data from the in vivo studies of muscle repair following injury in the mdx, WT eccentric damage mice. Based on the predicted human clearance value range of 5.7-19.5 mL/min/kg, a preclinical exposure target of 0.176 µg·h/mL and a conservative oral bioavailability range of 39% to 100%, the dose to achieve the therapeutic exposure target ranged from 4 to 37 mg. Based on the most conservative estimates, this AUC(0-t) value (0.176 µg·h/mL) is 63-fold and 328-fold lower than the AUC(0-t) value of female dog NOAEL and single dose stopping limit, respectively. The predicted Cmax value from the 37 mg (higher dose: Pred

Cmax=0. 0925μg/mL) is about 29-fold and 108-fold lower than the Cmax value of NOAEL and single dose stopping limit, respectively.

Assumptions were made on the following PK and PD parameters in order to bridge from animal to man: CL, V, F and in vivo ED_{50} of H-PGDS. These assumptions will be verified with lower dose data and if needed, adjustments will be made in subsequent dose selections.

4.3.3. Minimum Anticipated Biological Effect Level (MABEL) Dose

A 10% inhibition of the H-PGDS enzyme (IC_{10}) was considered as the MABEL and the PK of lower GSK3439171A was simulated in a 70-kg human using an estimated median clearance (CL) (10.8 mL/min/kg) and V (4.6 L/kg) with 30% between-subject variability assuming a 1-compartment model. A single dose of 5 mg was predicted to maintain IC_{10} levels (0.86 ng/mL) and a reasonable concentration is expected to be above the lower limit of quantification (LLOQ). This predicted AUC(0-t) value for 5 mg dose (0.1 μg·h/mL) is 110-fold lower than the NOAEL AUC(0-t) value and the predicted Cmax value (0.01 μg/mL) is about 270-fold lower than the NOAEL Cmax value.

4.3.4. Dose Predicted to Achieve Exposure at the NOAEL Dose Level and Single Dose Stopping Limit

Based on the predicted human clearance value range of 5.7-19.5 mL/min/kg, a conservative range of oral bioavailability from 39% to 100%, and a NOAEL AUC(0-t) value of 11 μg·h/mL, the dose to achieve the female dog NOAEL exposure level ranges from 263 to 2310 mg. Also, the dose to achieve the Single Dose Stopping Limit exposure of 57.8 μg·h/mL ranges from 1384 to 12138 mg.

4.3.5. Summary

The MRSD is 66.7 mg, the dose to achieve the therapeutic target is 37 mg BID, and dose to achieve the female dog NOAEL exposure level ranges from 263 to 2310 mg. Based on MABEL dosing, the starting dose will be 5 mg (13.34-fold lower than MRSD). Further dose escalation will be based on exposure, safety, and tolerability from the previous dose level. Based on the range of predicted H-PGDS inhibition and NOAEL exposure cover, the expected top dose may be 500 mg and the maximum dose that can be administered based on the Genotoxic Risk Assessment (GRA) is 3000 mg.

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 or the last scheduled procedure shown in the SoA.

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 enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 65 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, 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 ≥50.0 kg (110 lbs.) and body mass index (BMI) within the range 18.5 to 31.0 kg/m^2 (inclusive).

Sex

4. Only males are eligible for this study

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

Male participants are eligible to participate if they agree to the following during their entire enrolment in the study plus an additional 5 days or 5 terminal half-lives (whichever is longer)

- Refrain from donating sperm

PLUS either:

- Be abstinent from sexual 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

female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4.

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, renal, gastrointestinal, endocrine, hematological, 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. Any clinically significant abnormal vital signs
3. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
4. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
5. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
7. QTc >450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.

Prior/Concomitant Therapy

8. Unable to refrain from the use of aspirin, NSAIDs, vitamins, herbal and dietary supplements (including St John's Wort) within 10 days prior to the first dose of study medication (Specific medications listed in Section 6.5 may be allowed).

Prior/Concurrent Clinical Study Experience

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

Diagnostic assessments

12. Presence of Hepatitis B surface antigen (HBsAg) at screening
13. Positive Hepatitis C antibody test result at screening.

NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C ribonucleic acid (RNA) test is obtained

14. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention

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

15. Positive pre-study drug/alcohol screen
16. Positive human immunodeficiency virus (HIV) antibody test

Other Exclusions

17. Regular use of known drugs of abuse or positive urine drug test at screening or each in-house admission to the clinical research unit
18. Regular alcohol consumption within 6 months prior to screening and 5 days prior to admission defined as:
    - An average weekly intake of > 14 units for males. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of 80 proof distilled spirits.
19. Positive urinary cotinine test indicative of smoking history at screening or 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.
20. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- 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 start of study intervention until after the final dose.
- In Parts A and B, participants will fast at least 10 hours prior to dose and no food is allowed until 4 hours post-dosing. Meal times should be approximately uniform across all treatment periods. See the study reference manual (SRM) for additional details.
- Water is allowed as desired except one hour before and after dosing.
- In Part B, a subset of participants will undergo biliary metabolism testing using the Enterotest. The string device will be swallowed approximately 2 hours post-dose and removed at approximately 7 hours post-dose. At approximately 6 hours post-dose (i.e. ~1 hour prior to string withdrawal), a food cue will be used to stimulate gall bladder emptying and to encourage the release of bile onto the string:
    - Participants will be provided with visual images of food and asked to imagine eating the food for approximately 60 seconds.
    - Participants will then sniff a piece of orange peel/zest for approximately 30 seconds.
    - Participants will consume a high-fat food morsel (e.g. sausage sandwich) in order to stimulate gallbladder contraction

  Additional details on this procedure are available in the SRM
- In Part C, 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 1 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. Non-compliance will be recorded as well as the amount of the meal not eaten.
- The high fat/high calorie meal provided in the Fed arm of Part C 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 as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.

Table 1 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

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will 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 PK and/or PD sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.
- Participants will refrain from smoking or using tobacco or nicotine-containing products from at least 6 months prior to the Screening Visit through the last blood sample collected.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 72 hours before each admission to the unit and throughout their stay in the unit. Participants may participate in light recreational activities during studies (e.g., watching television, reading). Participants will also abstain from strenuous exercise for 72 hours before their follow-up visit.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 only 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. Rescreened participants should be assigned a new participant number.

Subjects who screen in one Part will not need to be rescreened for another Part, as long as they are within the 30 day screening window. A new subject number and rescreening will only be needed if they are outside the screening window.

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

ARM Name	Experimental	Control
Intervention Name	GSK3439171A	Placebo
Type	Drug	Drug
Dose Formulation	Oral solution (doses 0.5 mg up to 4.5 mg) capsule (doses 5 mg and upwards)	Oral solution to match experimental (doses 0.5 mg up to 4.5 mg) capsule (doses 5 mg and upwards)
Unit Dose Strength(s)	TBD	N/A
Dosage Level(s)	0.5 mg to not greater than 3000 mg (based on GRA limits) once or twice daily	Dosage and frequency to match experimental
Route of Administration	oral	oral
IMP and NIMP	IMP	NIMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention for solutions, will be provided in amber glass bottles with a child resistant cap. Each amber glass bottle will be labeled as required per country requirement. Study Intervention for capsules, will be provided in HDPE bottles with a child resistant cap. Each HDPE bottle will be labeled as required per country requirement.	Study Intervention for solutions, will be provided in amber glass bottles with a child resistant cap. Each amber glass bottle will be labeled as required per country requirement. Study Intervention for capsules, will be provided in HDPE bottles with a child resistant cap. Each HDPE bottle will be labeled as required per country requirement.

6.2. Preparation/Handling/Storage/Accountability

Details on storage, handling, and allowable excursions for GSK3439171A investigational product (IP), placebo, and solutions are provided in the Technical Agreement.

1. A description of the detailed methods and materials required for preparation of GSK3439171A solution or capsule and placebo are provided in the Technical Agreement.

2. The solution and capsules will be extemporaneously prepared at the clinical site as per instructions in the Technical Agreement 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.

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precaution will be taken to avoid direct contact with the study intervention. A MSDS 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

6.3.1. Randomization

Study using Pre-Coded Randomization provided to site	Before treatment begins at the beginning of each part of the study, participants will be assigned a unique number (randomization number) in ascending numerical order at the study site. The randomization number encodes the participant's assignment to the respective arms of the study, according to the randomization schedule generated prior to the study by the Clinical Statistics Department at GSK. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number throughout the study.

In Part A, approximately 9 participants in each cohort will be randomized to one of 3 treatment sequences (AAP, APA & PAA, where A represents an active dose of GSK3439171 and P represents placebo). Within each period, allocation of active (A) to placebo (P) treatment will be 2:1. Within a cohort, an increasing dose of GSK3439171A will be administered in each period as illustrated in the table below. Planned doses are provided in Section 6.6. At each dose level, sentinel dosing will be employed, such that one subject is dosed with placebo and another with active dose of GSK3439171A and followed for 48 hr prior to the rest of the subjects receiving their randomized treatment.

Cohort	Sequence	Period 1	Period 2	Period 3
Cohort 1	AAP	D1	D2	Placebo
	APA	D1	Placebo	D3
	PAA	Placebo	D2	D3
Cohort 2	AAP	D4	D5	Placebo
	APA	D4	Placebo	D6
	PAA	Placebo	D5	D6
Cohort 3	AAP	D7	D8	Placebo
	APA	D7	Placebo	D9
	PAA	Placebo	D8	D9

In each cohort of Part B, approximately 12 participants will be randomized to receive either GSK3439171A or placebo in a parallel design using a 3:1 allocation ratio. Participants will receive a single dose followed by a 72 hr assessment period and then will receive daily repeat doses until the end of the study.

Dose Cohort	Regimen
B1	R1 mg GSK3439171A or placebo QD or BID
B2[1]	R2 mg GSK3439171A or placebo QD or BID
B3[1]	R3 mg GSK3439171A or placebo QD or BID

1. Dose levels for Cohorts will be determined based on real-time analysis of the safety, tolerability, PK, and preliminary PD data from Part A and therefore may be adjusted from predicted dose levels listed.

QD – Once daily
BID- Twice daily

Regimen	Period 1	Period 2
X	GSK3439171A[1] administered in the fasted state	GSK3439171A[1] administered after a high fat meal
Y	GSK3439171A[1] administered after a high fat meal	GSK3439171A[1] administered in the fasted state

1 Dose to be determined based on data from Part A of the study

In Part C, approximately 12 participants will be randomized 1:1 to receive GSK3439171A in one of two treatment sequences (Fed then Fasted or Fasted then Fed).

Participants who do not complete the study may be replaced at the discretion of the investigator in consultation with the sponsor.

6.3.2. Blinding

Blind Break (Envelopes)	A sealed envelope that contains the study intervention assignment for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to GSK.

A participant may continue in the study if that participant's intervention assignment is unblinded.

Participants will be randomized to receive study intervention. Investigators and all site staff with the exception of the pharmacy staff will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, unblinded site pharmacy staff will be responsible for the dispensation of all study intervention and will endeavour to ensure that there are no differences in time taken to dispense following randomization. The site staff will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator.

Unblinded monitors and, in the event of a Quality Assurance audit, the auditor(s), will be allowed access to un-blinded study intervention 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 eCRF.

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.

Members of the GSK clinical study team will be unblinded for dose-escalation data reviews. This team may include but is not limited to the study statistician, programmers, physician project leader, Muscle Metabolism Discovery Performance Group leader, Clinical Investigation Lead, Operations Science Lead, Data Quality Lead, pharmacokineticist, DMPK analyst, safety review team, and other decision makers. At the time of the data reviews, access to the randomization will be restricted to randomization numbers that have been assigned to participants in the cohort(s) under review.

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 enrollment 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.

Participants must abstain from taking prescription or nonprescription drugs, including vitamins and dietary or herbal supplements (including St. John's Wort) within 10 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Due to potential effects on GSK3439171A's related pathways, neither aspirin nor NSAIDS of any kind are permitted for use from 10 days prior to the start of the study through the follow-up visit. Acetaminophen or another medication selected by the investigator and the Medical monitor may be administered as prescribed (acetaminophen not to exceed 4,000 mg/24 hr per current guidelines) by attending study staff if simple analgesia is required during the study. Local anaesthesia will be used for muscle biopsy procedures. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

6.6. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule, number of participants, and number of cohorts needed based on the emerging safety, PK, and PD data, but the maximum daily dose and/or (predicted) maximum/cumulative exposure will not exceed 3000 mg (based on GRA limit), 57.8 µg·h/ml for single dose AUC exposure limit in Part A (based on liver effects in dog at 600 mg/kg male dog), or 11.0 µg·h/ml for repeat dose AUC exposure limit in Part B (based on mean NOAEL exposure for liver effects in 20 mg/kg female 6-week dog study) respectively. The AUC stopping exposure limit of 11 µg.hr/mL s for the repeat dose phase were set by the rat adrenal toxicity is below (0.24 times) the lowest effect exposure for rat adrenal toxicity

Information regarding dose escalation review processes is detailed in the Dose Escalation Plan. Briefly, the GSK medical monitor, in joint discussion with the participating investigator(s) (to remain blinded during the study), will be responsible for making dose escalation decisions. Prior to the dose escalation decision, the GSK clinical team, which includes but is not limited to, the medical monitor, clinical scientists, safety physician and/or representative, and clinical pharmacokineticist, will review critical safety data defined in Section 8.2, Section 8.3, and in the Dose Escalation Plan. This includes review of all adverse events including non-dose-limiting toxicities, laboratory assessments and

other defined safety evaluations, as well as PK and PD data when appropriate. Quality control of critical safety data will also be described in the Dose Escalation Plan, which includes ongoing study monitoring visits, Sponsor review of the clinical database, and confirmation by site investigators and/or delegates that the data are accurate and complete.

The dose-escalation decision and rationale for each cohort will be discussed with the investigator(s) during teleconference(s) and documented in writing, with copies maintained at each study site and in the study master file.

The decision to proceed to the next higher dose level will be made by the clinical study team in consultation with the investigator(s) based on the evaluation of data from at least 4 participants (Part A) or 6 participants (Part B) who received active treatment at the preceding lower dose. Such decisions will be based on the safety and tolerability, as well as PK data observed at the lower dose level and the predicted exposure at the next dose level. Some doses may be deleted and intermediate and/or higher/lower doses may be added as appropriate during the study as the results of safety/tolerability, PK, and PD assessments become available.

The details on the dose escalation committee can be found in Section 9.5.1

6.6.1. Dose Escalation in Part A

In Part A, the decision to proceed to the next dose level of GSK3439171A will be made based on evaluation of the safety, tolerability and preliminary PK data as outlined in Section 4.1.

The primary preclinical exposure parameter that will guide dose escalation in Part A is based on single dose exposure limit in the male dog at 600 mg/kg/day (AUC(0-24h)) at steady state – 57.8 µg.h/mL described in Section 4.3. Assuming time-invariance, the Day 1 AUC(0-inf) observed in each of the human participants in this study at each single dose will be compared to the above value in order to determine the magnitude of dose escalation.

The following algorithm will be used for dose escalation in Part A:

1. For each dose group, the human mean AUC (0-inf) on Day 1 will be calculated as percentage of the male dog at 600 mg/kg/day of AUC(0-24) steady-state (57.8 µg·h/mL). Example dose escalation based on single dose exposure limit exposures is provided below. Some of the above doses may be deleted and intermediate and/or higher doses may be added as appropriate during the study as the results of safety/tolerability and PK assessments become available. The next dose level can then be determined as described in the example table below:

Table 2 Mean simulated exposures at SD of GSK3439171A compared to single dose exposure limit set by male dog at 600 mg/kg/day exposures levels

Dose (mg)	Mean Simulated AUC(0-inf) (µg*h/mL)	Fold cover from 600 mg/kg male dog AUC(0-24)[1]	Mean Simulated Cmax (µg/mL)	Fold cover from 600 mg/kg male dog Cmax[1]	Simulated % H-PGDS inhibition maintained for 24 hours[2]
5	0.10	578	0.01	1000	10
20	0.39	158	0.05	200	20
50	0.99	58	0.12	83	40
100	1.97	29	0.24	42	60
300	5.91	10	0.72	14	80
500[a]	9.85	6	1.20	8	85

[1] Compared to systemic exposure at 600 mg/kg/day in male dog steady-state AUC(0-24) and Cmax values (57.8 µg*h/mL and 10 µg/mL, respectively)

[2] Represents the simulated mean GSK343171A concentrations maintained at different H-PGDS inhibition levels over 24 hours

Fewer or more dose levels may be explored based on emerging data from Part A.

2. The highest dose in Part A will not exceed 3000 mg based on GRA limits.
3. The highest predicted mean Day 1 AUC (0-inf) in Part A will not exceed 57.8 µg·h/ml.

Dosing in Part C (food effect) can be initiated after the exposures achieved with at least two dose levels administered in a fasted state are calculated. The dose levels chosen for Part C will ensure an adequate safety margin to allow for an increased exposure of GSK3439171A in the presence of food.

6.6.2. Dose escalation in Part B

Part B can be initiated after the safety and PK data of at least four dose levels from Part A are evaluated. The decision to initiate Part B will be made by the clinical study team in conjunction with the investigator.

Dose selection in Part B will be based on the safety/tolerability and PK data from Part A. The following rules will guide dose selection in Part B:

1. The starting daily dose in Part B will be selected such that its predicted exposure (mean AUC(0-24) and Cmax) on the last day of dosing is no higher than the Day 1 exposure of a dose that has been found to be well tolerated and had no safety signals of concern in Part A. As the highest exposure with repeat dosing is expected on the last day of dosing (as a result of accumulation), this approach would select a daily dose which provides blood concentrations that, at any time during the period of dosing, are no higher than the ones already found to be well tolerated and had no safety signals of concern in Part A. The expected exposure on the last day of dosing

will be predicted based on the PK parameters for GSK3439171A established in Part A.

2. Subsequent doses in Part B may be selected using the criteria described above for the starting dose. Alternatively, a dose may also be selected even if it does not meet these criteria provided it is no more than 4-fold higher than a previous dose that has been found to be well tolerated and had no safety signals of concern upon repeat dosing in Part B.
3. The highest daily dose in Part B will not exceed the highest single dose that has been found to be well tolerated and had no safety signals of concern in Part A.
4. The highest predicted mean AUC(0-24) on the last day of dosing in Part B will not exceed 11.0 μg·h /ml (based on mean NOAEL exposure for liver effects in 20 mg/kg female 6-week dog study and is below (0.24 times) the lowest effect exposure for rat adrenal toxicity).

6.7. Intervention after the End of the Study

Not applicable.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

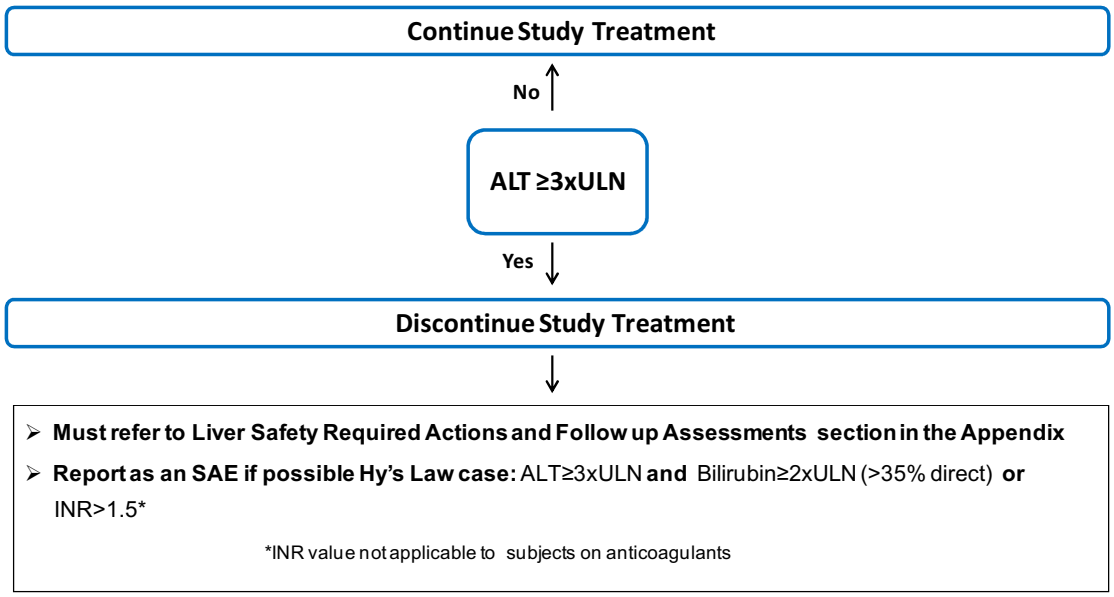
7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study and followed appropriately until 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.

7.1.1. 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.

7.1.1.1. 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.

7.1.2. QTc Stopping Criteria

- The QTcF formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.

  - For example, if a participant is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual participant as well.
  - The QTcF formula must be used for a participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on the average of triplicate ECG readings obtained over a brief (e.g., 5-10 minute) recording period.

A participant that meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study intervention.

- QTcF >500 msec,
- Change from Baseline: QTc >60 msec

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

7.1.3. 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 (as defined in CTCAE v5.0) that is considered attributable to dosing with GSK3439171A will be withdrawn from the study.

7.1.4. Dose Adjustment/Discontinuation Pharmacokinetic Criteria

In part A, any participant with observed AUC(0-inf) or Cmax values greater than the mean steady-state AUC(0-24) and Cmax values in male dog (57.8 µg·h/mL and 10 ug/mL, respectively) will be discontinued from study intervention.

In Part B, any participant with observed AUC(0-24) value greater than the mean steady-state AUC(0-24) observed in female dogs (11.0µg·h/mL) will be discontinued from study intervention.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.5. Temporary Discontinuation

Temporary discontinuation of the study intervention is not allowed.

7.1.6. Study Stopping Criteria

7.1.6.1. Safety Study Stopping Criteria

Dosing at the currently tested dose as well as escalation to higher doses will be stopped if either of the following occurs in the current dose group:

- An SAE that is considered to be related to GSK3439171A in one or more participants on active treatment.

- Similar AEs of moderate or severe intensity (as defined in CTCAE v5.0) that are considered to be related to GSK3439171A in two or more participants on active treatment.

Dosing at the current (or higher) dose may resume only if a safety review conducted by GSK in conjunction with the investigator determines that the observed SAEs or AEs are not related to GSK3439171 and such resumption is approved by the IRB/IEC.

7.1.6.2. PK Study Stopping Criteria

The single dose PK stopping criteria are based on AUC(0-24) from the 600 mg/kg/day male dog due to liver findings. It is planned that for Part A, the predicted human mean GSK3439171A AUC(0-inf) or Cmax values will not exceed the mean GSK3439171A steady-state AUC(0-24) and Cmax values in male dog (57.8 ug·h/mL and 10 ug/mL, respectively).

The repeat dose PK stopping criteria are based on AUC(0-24) from the 20 mg/kg/day female dog NOAEL due to liver findings. It is planned that for Part B, the predicted human mean GSK3439171A AUC(0-24), value will not exceed the mean GSK3439171A steady-state AUC(0-24) values in dog at 20 mg/kg/day of 11.0 ug·h/mL.

7.2. 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, behavioral, 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, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued 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.

7.3. Lost to Follow Up

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

The following actions must be taken if a participant fails to return to the 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 or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole 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.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed 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 preceded by at least 5 minutes of rest in a supine position for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate. Three readings of blood pressure and pulse will be recorded at intervals 1 to 2 minutes apart as specified in the SoA. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the case report form (CRF).

8.2.3. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECGs will be recorded whilst the participant is in a supine position, having rested in this position for at least 15 minutes. Participants are permitted to make intermittent movement, if necessary, in preparation for procedures (e.g., to sit up to take study medication). When ECGs are to be taken in triplicate, an interval of at least 5 minutes will be used between measures taken at screening or pre-dose. An interval of at least 1 minute is acceptable for any post-dose triplicate ECGs, when needed.

- Various values from the ECG read-out will be entered into the eCRF (the average for some will be used for measures made in triplicate).
- Any result falling outside the expected normal ranges as defined by the site will be repeated at the discretion of the investigator. If any results falling outside of these expected normal ranges at the site are deemed not clinically significant by the investigator or an appropriately qualified designee, then this should be clearly stated on the hard copies of the ECG and signed and dated by the investigator.
- If the ECG trace indicates an abnormality that is measured by the equipment but is deemed normal by the investigator, then this should be clearly stated on the ECG tracing as normal and signed and dated by the investigator or appropriately qualified designee. If the ECG tracing indicates an abnormality that is present but deemed as not clinically significant by the investigator or appropriately qualified designee, then this should be clearly stated on the ECG tracing as "NCS" and signed and dated by the investigator or appropriately qualified designee and stored with the source records for that participant. If any results falling outside of the normal ranges are deemed clinically significant by the investigator or appropriately qualified designee then these should be recorded in the eCRF as an AE.
- ECGs will be stored electronically for manual measurement of intervals, if necessary.
- Whenever a 12-lead ECG is scheduled at the same nominal time as other study procedures (including vital signs, blood draws, or meals), the ECG should be obtained first followed by other procedures with timing planned so that the blood draw occurs at the exact nominal time.

8.2.4. Telemetry

Telemetry will be performed during the study as outlined in the SoA. Additional details are available in the SRM.

8.2.5. Holter Monitoring

Cardiac monitoring (24 hour) will be performed using continuous Holter monitoring during the study as shown in the SoA.

Start date and time and stop date and time will be captured in the study database. Analysis of the Holter monitoring will consider the following:

- Heart rate (HR) (brady and tachycardia).
- Normal and aberrant beats.
- Number of supraventricular contractions, premature atrial contractions, supraventricular tachycardias, premature ventricular contractions, couplets, triplets and ventricular tachycardias.
- Atrio-ventricular conduction defects.

- Atrial fibrillation and flutter.

8.2.6. 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. Any lab or clinical assessment that is judged to be spurious by the Principal Investigator (PI) may be repeated.
- 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 SoA.
- Samples collected for hematology, clinical chemistry, urinalysis, or hormone assays will be analysed at the unit's local laboratory under the relevant Standard Operating Procedures (SOPs), GUIs and user manuals. See user local laboratory manuals for details on methodology, processing, handling of specimens, and analyses.
- Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Appendix 2.

8.2.7. Hormone Monitoring

Based on preclinical findings in the rat Good Laboratory Practice (GLP) toxicology studies outlined in the IB, hormone monitoring will take place in Part B of the study only. Blood samples will be obtained as per the SoA and SRM and analysed for:

- Adrenal – ACTH, cortisol
- Pituitary – LH, FSH, TSH, T3, and free T4
- Total Testosterone and DHT

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or until the final follow up visit 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

within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

8.2.8. Suicidal Ideation and Behaviour Risk Monitoring

Not applicable.

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 start of intervention 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 participant 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 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 7.3). 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, Institutional Review Boards (IRB)/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 IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until follow-up.
- 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 SAE.

8.4. Treatment of Overdose

For this study, any dose of GSK3439171A greater than 3000 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:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK3439171A can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of GSK3439171A 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. 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.
- In Part B, at each sampling time point an additional 2 mL blood will be collected for metabolite profiling. Results will be reported under a separate PTS-Global Spectroscopy, GSK protocol.
- Samples will be used to evaluate the PK of GSK3439171A. 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.
- 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.

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

8.5.2. Urine Sample Collection

In Part B only, urine samples will be collected as outlined in the SoA and urine PK calculations of GSK3439171A (including renal clearance), will be performed, as appropriate. These samples may also be analysed for additional metabolites of GSK3439171A as appropriate. The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

Prior to dosing on Day 1, urine samples will be collected for predose sampling as outlined in the SoA. Post-dose urine collection time points listed in the SoA table will begin immediately following dose administration. 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. Subaliquots of these samples may be assessed for pharmacodynamics and results will be reported under a separate protocol. Details of urine sample processing, storage and shipping procedures are provided in the SRM or equivalent.

8.5.3. Bile Sample Collection

The Entero-Test will be administered to the second or third dose cohort in Part B (depending on PK results in Part A) as outlined in the SoA. The Entero-Test is a gelatin capsule containing a weighted nylon line. The Entero-Test will be swallowed approximately 2 hours after dosing by the fasted subject with one end taped to the face. Once the capsule has dissolved in the stomach, the weighted string will pass into the duodenum. The weight will detach from the string and passed into stool. During the post-dose period, bile flow will be promoted while the string is in the duodenum with a food stimulus at approximately 6 hours following the morning dose. The string will be withdrawn from the oral cavity approximately 1 hour later.
The duodenal bile adsorbed to string will be eluted and analysed for drug-related peaks and the results reported under a separate PTS Global Spectroscopy, GSK protocol. The Entero-Test bile sample collected from placebo-dosed subjects will be considered as the control.

Additional details of the bile sample collection procedure, processing, storage and shipping procedures are provided in the SRM or equivalent.

8.5.4. Sample Analysis

Plasma, urine, and muscle (as appropriate) analysis will be performed under the control of PTS Bioanalysis, US, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK3439171A will be determined in plasma, urine, and muscle samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM) or equivalent.

Plasma, bile and urine samples may be analyzed for other compound-related metabolites and the results reported under a separate PTS Global Spectroscopy, GlaxoSmithKline protocol.

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

8.6. Pharmacodynamics

Under guidance of the SRM or equivalent, samples will be shipped to GlaxoSmithKline or appropriate third-party vendors for analysis.

8.6.1. Urine Pharmacodynamics Assessment

Subaliquots of the urine samples collected in Parts A and B will be designated for measurement of prostaglandin and/or inflammatory PD markers, including but not limited to tPGDM and tPGEM, at the time points outlined in the SoAs in Section 1. See SRM (or equivalent) for details on sample collection, processing, and storage.

8.6.2. Muscle Biopsy

Muscle biopsies will be obtained in order to examine PK/PD of GSK3439171A as well as H-PGDS inhibition in a tissue of potential relevance. Information gained from these biopsies will also help in determining dose selection for future studies. Under local anesthesia, skeletal muscle biopsies will be obtained from the vastus lateralis at the time points indicated in Part B of the SoA. See SRM or equivalent for details on the procedure, sample collection, and storage.

8.7. Genetics

A 6 mL blood sample for deoxyribonucleic acid (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 and destruction of these samples can be found in the SRM or equivalent.

8.8. Biomarkers

Collection of samples for other biomarker research is also part of this study. Refer to the SoA and SRM (or equivalent) for details on timings.

These samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to prostaglandin and/or inflammatory-mediated diseases.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of biomarker responses to GSK3439171A.

8.9. Health Economics or Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objectives of this study are to evaluate safety and tolerability of single and repeat doses of GSK3439171A and to characterize the PK of GSK3439171A. No formal statistical hypotheses will be tested. Descriptive statistics will be used to assess safety and tolerability objectives. Treatment comparisons with placebo will be based on review of descriptive statistics and individual participant data. An estimation approach will be used to address the PK objectives where point estimates and corresponding 90% confidence intervals (CIs) will be constructed as appropriate for the assessment of dose-proportionality, steady-state, time invariance and food effect.

Estimation of effects of GSK3439171A on PD/biomarkers is an exploratory objective. No formal statistical hypotheses will be tested. An estimation approach will be used to address these objectives, where point estimates and corresponding CIs will be constructed as appropriate.

Unblinded, in-stream data reviews will be performed for Parts A and B in order to inform dose-escalation decisions. Final results for each study part (A, B, C) may be reported as each part completes rather than after completion of all study parts.

9.2. Sample Size Determination

The sample size for the study is not based on statistical considerations. The sample size for Part A (single dose, dose-escalation) has been selected to provide sufficient safety, tolerability and PK data to support escalation to the next single dose level in Part A and to support selection of dose levels for Part B while minimizing the number of participants exposed to study drug. Similarly, the sample size for Part B (repeat dose, dose-escalation) has been selected to provide sufficient safety, tolerability and PK data to support escalation to the next repeat dose level in Part B and to support dose selection for subsequent studies.

The sample size for Part C (food effect) was selected in the absence of estimates of variability for PK parameters as the minimum needed to adequately estimate food effect and may be re-estimated based on the observed PK variability from Part A.

Approximately 150 participants will be screened to achieve 75 randomly assigned to study intervention and 75 evaluable participants for an estimated total of 27 evaluable participants in Part A (6 active: 3 placebo per cohort), 36 evaluable participants in Part B (9 active:3 placebo per cohort), and 12 evaluable participants in Part C.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who were randomized
Evaluable	All randomized participants who take at least 1 dose of study intervention and undergo at least one set of assessments.
Safety	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
PK	Participants in the Safety population for whom a PK sample was taken and analyzed for GSK3439171A and result reported
PD	Participants in the Safety population with Baseline and at least one post-Baseline PD measure.

9.4. Statistical Analyses

Pharmacokinetic Analyses

PK analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, CPMS, GlaxoSmithKline. Plasma GSK3439171A concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.2 or higher. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following PK parameters will be determined, as data permit:

- Apparent Clearance (CL/F)
- maximum observed blood concentration (Cmax),
- time to Cmax (tmax),
- area under the plasma concentration-time curve [AUC(0-t), AUC(0-inf) and AUC(0-τ)]
- apparent terminal phase half-life ($t_{1/2}$)
- trough concentration (C_τ).

AUC(0-∞) or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality. Trough concentration (C_τ) samples collected on the specified days will be used to assess attainment of steady state and the steady state ratio

(R_{ss}) will be calculated (Day 16 AUC(0-τ)/Day 1 AUC(0-inf)). To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro: Day 13 or 17 AUC(0-τ)/Day 1 AUC(0-τ); and RCmax: Day 13 or 17 Cmax/Day 1 Cmax) will be determined.

PK data will be presented in graphical and/or tabular form and will be summarized descriptively.

Statistical analyses of the PK parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline. Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If there are any important departures from the distributional assumptions, alternative models may be explored using appropriately transformed data. Full details on the statistical aspects will be described in the Reporting and Analysis Plan (RAP).

Dose Proportionality (Parts A and B: Single and Repeat Dose Study Phases)

Dose proportionality will be assessed following single doses of GSK3439171A (Part A) via analyses of AUC(0-t), AUC(0-inf), and Cmax. Dose proportionality following repeated dosing (Part B) will be assessed using AUC(0-τ) and Cmax.

A statistical analysis will be performed for each parameter separately using the power model with the log-transformed PK parameter as the dependent variable and log(dose) as a fixed effect. For Part A, the intercept and slope will be fit as random effects. In addition, effects for cohort and cohort by log(dose) may be included in the model to examine differences in slopes across cohorts. Estimates of the slopes will be reported along with corresponding 90% CIs (slope≈1 implies dose proportionality).

Food Effect (Part C: Single Dose Study)

The effect of food on the PK of GSK3439171A (AUC(0-inf), Cmax, and $t_{1/2}$) will be examined. An analysis of variance model will be fitted separately to each of the log-transformed PK parameters with period and treatment (fed or fasted) as fixed effects and participant as a random effect. Point estimates for the differences in means (GSK3439171A fed – GSK3439171A fasted) and corresponding 90% CIs will be constructed from the least squares means, using the residual variance. These will then be back-transformed to provide point estimates and corresponding 90% CIs for the ratio of geometric means fed:fasted.

Accumulation (Part B: Repeat Dose Study Phase)

The extent of accumulation of GSK3439171A will be based on AUC (Ro) and Cmax (RCmax).

Statistical analysis of log-transformed AUC(0-τ) and Cmax will be performed separately and by dose using an ANOVA model with a fixed, categorical effect for day and a random effect for participant. The accumulation ratios (Ro and RCmax) of

GSK3439171A will be evaluated for each dose by exponentiating the difference in least squares means (Day 13 or 17 – Day 1) and the associated 90% CI.

Time Invariance

Assessment of the achievement of steady state will be based on the AUC (Rss). The time invariance ratio will be calculated as the ratio of AUC(0-τ) on Day 13 or 17 over AUC(0-inf) on Day 1. The time invariance ratio will be listed and summarized along with other PK parameters.

Statistical analysis of the log-transformed AUCs will be performed separately for each dose using an ANOVA model with a fixed, categorical effect for day and a random effect for participant. The time invariance ratio of GSK3439171A will be evaluated for each dose by exponentiating the difference in least squares means (Day 17 – Day 1) and the associated 90% CI. The values of AUC used in the analysis will be AUC(0-inf) on Day 1 and AUC(0-τ) on Day 13 or 17.

Achievement of Steady State (Part B: Repeat Dose Study Phase)

Steady-state will be assessed visually by plotting trough concentration levels, C_τ, collected pre-morning dose versus collection day by dose. In addition, statistical analysis of trough concentration levels (e.g., Days 6,7,9, and 10 (7 day repeat dosing period) or 6-7, 16-17 (14 day repeat dosing period) will be performed after log-transformation of the concentrations. A mixed effects ANOVA model will be fit with day (continuous variable) as a fixed effect and subject as a random effect for each dose level separately. The coefficient for the slope of the day effect on the log-scale will be used to evaluate steady state for each dose. The 90% confidence intervals for the slope will be calculated.

9.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics will be used to assess safety and tolerability objectives. No formal statistical analyses of safety data are planned. Data will be summarized according to GSK Integrated Data Standards Library (IDSL) standards. In addition, individual participant data will be reviewed. Treatment comparisons with placebo will be based on review of descriptive statistics and individual participant data.

9.4.2. Other Analyses

In Parts A and B, dose-response modelling of urinary tPGDM/tPGEM will be undertaken, data permitting. Details will be described in the reporting and analysis plan. The population PK analysis and pharmacodynamic analyses may 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, PK, and PD/biomarker 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 treatment group and graphical displays. This is a sponsor unblinded trial and GSK staff will be unblinded for these reviews (see Section 6.3).

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.

9.5.1. Data Monitoring Committee (DMC)

Dose modifications, including dose escalations, will be reviewed by the dose escalation committee. This committee includes, but is not limited to, the medical monitor, principal investigator, clinical scientists, safety physician and/or representative, and clinical pharmacokineticist. Dose escalation decisions will be made as outlined in Section 4.1 and Section 6.6 and in 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 IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

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 IRB/IEC members, and by inspectors from regulatory authorities.

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.

10.1.5. 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
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.6. 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, IRB/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.

10.1.7. 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 Document Agreement.

10.1.8. Study and Site Closure

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

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

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

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

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 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.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Table 3 Protocol-Required Safety Laboratory Assessments

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin	Prothrombin time (with and without INR)	Eosinophils
Hematocrit	Activated partial thromboplastin time	Basophils

Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
			Creatine Phosphokinase (Total)

Hormone Assessments

Luteinizing hormone (LH)	Total Testosterone	Adrenocorticotropic hormone (ACTH	cortisol	Free T4
Follicle stimulating hormone (FSH)	Dihydrotestosterone (DHT)	Thyroid stimulating hormone (TSH)	T3	

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)

Other screening tests

HIV
Hepatitis B (HBsAg)
Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) should be reflexively performed **on the same sample** to confirm the result)
Cotinine, Serum Alcohol, and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).

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 7 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 IRB/IEC.

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

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.

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 Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety

assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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 fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

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 (eg, 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 (eg, 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 has occurred and the investigator has minimal information to include in the initial report to GSK. However**, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any 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 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**.
- 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 the Study Reference Manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED FOR FEMALE PARTNERS OF PARTICIPANTS 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. 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)

10.4.2. 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 GSK3439171A.
- 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 IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3439171A or prostaglandin or inflammation-mediated disease. They may also be used to develop tests/assays including diagnostic tests) related to GSK3439171A or study interventions of this drug class and prostaglandin or inflammation-mediated disease. 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 GSK3439171A 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 GSK3439171A (or study interventions of this class) or prostaglandin or inflammation-mediated disease 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="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>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="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event 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 subject 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 hrs
• Monitor subjects 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 INR ≤1.5:

• Repeat liver chemistries (include ALT, AST,</td><td>• 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

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:

• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within Baseline	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]. **NOTE: not required in China.** • 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 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 subjects 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 subject'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: Abbreviations and Trademarks

Abbreviations

µg	microgram
ACTH	Adrenocorticotropic Hormone
AE	adverse event
ALKP	Alkaline Phosphatase
ALT	Alanine Transferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum Concentration
CO2	Carbon Dioxide
CONSORT	Consolidated Standards of Report Trials
COX	Cyclooxygenase
CPMS	Clinical Pharmacology Modelling and Simulation
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTFF	Clinical Trial Facilitation Group
C_τ	Trough Concentration
CV	Cardiovascular
D	Dose
DHT	Dihydrotestosterone
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ED50	Median Effective Dose
Emax	Maximum Efficacy
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
FTIH	First Time In Human
g	Gram
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma-glutamyl Transferase
GLDH	Glutamate Dehydrogenase

GLP	Good Laboratory Practice
GRA	Genotoxic Risk Assessment
GSK	GlaxoSmithKline
GUIs	Guidances
HBCAb	Hepatitis B Core Antibody
HBSAg	Hepatitis B Surface Antigen
HED	Human Equivalent Dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
H-PGDS	Hematopoietic Prostaglandin D2 Synthase
hr	hours
hr^{-1}	Per hour
HR	Heart Rate
IB	Investigator's Brochure
IC	Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Internal Ethics Committee
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Internal Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
kg	Kilogram
KO	Knockout
L	Liter
LAM	Lactational Amenorrhea Method
lb	pound
LBF	Liver Blood Flow
LH	Luteinizing Hormone
m^2	Square Meter
MABEL	Minimum Anticipated Biological Effect Level
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	milligram
min	minute
mL	Milliliter
MRSD	Maximum Recommended Starting Dose
MSDS	Material Safety Data Sheet
NCS	Not Clinically Significant

ng	nanogram
NIMP	Non-Investigational Medicinal Product
NOAEL	No Adverse Effect Level
NOEL	No Effect Level
NSAID	Non-steroidal Anti-inflammatory Drug
PBPK	Physiologically-based Pharmacokinetics
PD	Pharmacodynamics
PG	Prostaglandin
PGD2	Prostaglandin D2
PGE2	Prostaglandin E2
PGF2A	Prostaglandin F2a
PGG2	Prostaglandin G2
PGH2	Prostaglandin H2
pH	Potential of Hydrogen
PI	Principal Investigator
PK	Pharmacokinetics
PND	Post-Natal Day
PO	Per Oral
QT	QT Interval
QTc	Corrected QT Interval
QTcF	QT interval corrected according to Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cells
RCmax	Ratio of Cmax
RD	Repeat Dose
RNA	Ribonucleic Acid
Rss	Steady-state Ratio
SAE	Serious Adverse Event
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SD	Single Dose
SOA	Schedule of Activities
SOPs	Standard Operating Procedures
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	terminal half-life
T3	Triiodothyronine
T4	Thyroxine
Th2	T Helper 2
tPGDM	11,15-Dioxo-9α-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid
tPGEM	9,15-dioxo-11α-hydroxy-13,14-dihydro-2,3,4,5-tetranorprostan-1,20-dioic acid
tmax	Time to Maximum Observed Concentration

TSH	Thyroid Stimulating Hormone
TXA2	Thromboxane A2
ULN	Upper Limit of Normal
WBC	White Blood Cell
WT	Wildtype

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
PK Predictor Pro

Trademarks not owned by the GlaxoSmithKline group of companies
GastroPlus
WinNonlin

10.8. Appendix 8: 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: 31-AUG-2018

Overall Rationale for the Amendment: Updates to the PK exposure limits for Parts A and B, stopping criteria, and safety review language have been modified based on FDA recommendations. Day -2 has also been removed from Part C of the SoA as it is not necessary. Information around Holter Monitoring has been altered to reflect the intent of collecting but not analyzing Holter Monitoring data in this study.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA	Removal of Day -2 from Part C SoA	Participants will not be undergoing PD assessments in Part C and therefore Day -2 admission is not required
2.3 Benefit/Risk Assessment	Addition of clarification of minimum number and type of participants data for dose escalation review	A minimum of 4 participants on active treatment will complete all assessments as outlined. All available safety and PK data from all participants will be reviewed.
2.3.1 Risk Assessment	Update of information describing dose-limiting findings in preclinical species	The FDA has recommended a higher single dose limit above the dog NOAEL as the effects are monitorable in a clinical setting
4.3 Justification for Dose	Updates to dose exposure limits based on preclinical species data and resulting changes in MRSD and exposure limits for Parts A and B of the study	The acceptable exposure limits have been increased for Part A and decreased for Part B based on interpretation and clinical management of preclinical findings and pharmacokinetic modelling.

Section # and Name	Description of Change	Brief Rationale
6.6 Dose Modification	Changes to human exposure limits and planned doses updated	The acceptable exposure limits have been increased for Part A and decreased for Part B based on interpretation and clinical management of preclinical findings and pharmacokinetic modelling.
7.1.3 Individual Stopping Criteria	Stopping criteria described separately for both SAEs and AEs	Differences between SAEs, AEs, and automatic withdrawal from the study needed to be more discretely defined.
7.1.4 Dose Adjustment/Discontinuation Pharmacokinetic Criteria	PK stopping criteria updated based on updated exposure limits	The acceptable exposure limits have been increased for Part A and decreased for Part B based on interpretation and clinical management of preclinical findings and pharmacokinetic modelling.
7.1.7.1 Safety Study Stopping Criteria	Study Stopping criteria described separately for both SAEs and AEs	Differences between SAEs, AEs criteria for stopping the study need to be more discretely defined.
7.1.7.2 PK Study Stopping Criteria	PK study stopping criteria updated based on updated exposure limits	The acceptable exposure limits have been increased for Part A and decreased for Part B based on interpretation and clinical management of preclinical findings and pharmacokinetic modelling.
8.2.5 Holter Monitoring	Removal of data points from section	As Holter Monitoring will be collected and not analysed in this study, interpretation and nature of abnormalities will not be captured in the study database
Throughout	Minor editorial and document formatting revisions Updated the abbreviation table.	Minor, therefore have not been summarized Corrections/clarifications

Amendment 2: 13-MAR-2019

Overall Rationale for the Amendment: The safety study stopping criteria language has been updated to reflect the intention for the two or more AEs of moderate or severe intensity to be of similar kind. In addition, we have aligned the protocol to a previous

Note To File (NTF) updating the Schedule of Activities (SoAs), study design, statistical analyses and objectives and endpoints based on emerging PK data gathered during this study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis- Objectives	Addition of Ctrough concentrations at Dose 3 and 4	The PK of GSK3439171 is different than the initial preclinical predictions, leading to alterations of study assessment windows and PK timings that have previously been captured in a NTF
1.3 Schedule of Activities	Update to reflect changes made to study assessments based on emerging PK data	The PK of GSK3439171 is different than the initial preclinical predictions, leading to alterations of study assessment windows and PK timings that have previously been captured in a NTF
3 Objectives and Endpoints	Update to reflect changes made to study assessments based on emerging PK data	The PK of GSK3439171 is different than the initial preclinical predictions, leading to alterations of study assessment windows and PK timings that have previously been captured in a NTF
4 Study Design	Update to reflect changes made to study assessments based on emerging PK data	The PK of GSK3439171 is different than the initial preclinical predictions, leading to alterations of study assessment windows and PK timings that have previously been captured in a NTF
7.1 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	Update to language to specify occurrence of similar AEs	Safety study stopping criteria was intended to reflect the occurrence of similar AEs of moderate or severe intensity occurring in two or more participants.
9.4 Statistical Analyses	Update to reflect changes made to study assessments based on emerging PK data	The PK of GSK3439171 is different than the initial preclinical predictions, leading to alterations of study assessment windows and PK timings that have previously been captured in a NTF

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