TITLE PAGE

Protocol Title: A randomised double-blind, placebo controlled, single ascending and repeat dose, First Time in Human study in healthy participants and stable asthmatics to assess safety, tolerability and pharmacokinetics of GSK3923868 inhalation powder

Protocol Number: 213497/ Amendment 04

Compound Number or Name: GSK3923868

Brief Title: Safety, tolerability and pharmacokinetics of GSK3923868 inhalation powder in healthy participants and stable asthmatics.

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s):

EudraCT: 2020-002203-19

Approval Date: 24 Sep 2021

SPONSOR SIGNATORY:

Protocol Title: A randomised double-blind, placebo controlled, single ascending and repeat dose, First Time in Human study in healthy participants and stable asthmatics to assess safety, tolerability and pharmacokinetics of GSK3923868 inhalation powder

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The signed page is a separate document.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE.

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 04	*24 Sep 2021*	TMF-13791516
Amendment 03	*15-FEB-2021*	2020N430088_03
Amendment 02	*07-SEP-2020*	2020N430088_02
Amendment 01	*28-AUG-2020*	2020N430088_01
Original Protocol	*17-Jul-2020*	2020N430088_00

Amendment [04]: 24 Sep 2021

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

Overall Rationale for the Amendment

This amendment has been prepared to:

- Remove the requirement for bronchodilator reversibility for the SABA only using mild asthma population; as all participants will have a physician confirmed diagnosis of asthma at least 6 months prior to screening.
- Update to Part C inclusion criteria for SABA only population to also include intermittent ICS/LABA use, to align with current treatment guidelines. The regular ICS/LABA use population remains unchanged.
- Increase the maximum age of participation from 50 to 65 years of age, in line with the easing of some COVID 19 pandemic restrictions and the availability of safety and tolerability data. Participants over the age of 50 will need to provide proof of COVID-19 vaccination before being eligible to participate.
- Clarification to planned cohort 2, study intervention dose levels.
- Updated access to unblinded data from complete cohorts to include safety endpoints.
- Document the addition of a PK blood sample at 15 mins in Parts B and C (as per Section 8.3.1 Plasma Sample Collection), to support modelling of PK data.

Specific details of the changes are provided below:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA), Parts B & C	Addition of 15 mins PK blood sample.	To support modelling of PK data.
Section 4.1 Overall Design, Part C: Repeat Dose in Participants with Asthma (Parallel Group),	Updated 'SABA only' treatment to include treatment with 'intermittent' ICS/LABA	Population treatment requirements updated in line with updated treatment guidelines.
Section 5.1.2 Inclusion Criteria: Part C (Participants with Asthma), number 1	Increase to maximum age of participation, from 50 years to 65 years.	Currently, COVID 19 pandemic restrictions have been lifted within the UK and safety data has been generated from healthy participants, with no safety concerns identified. The increase in maximum age of participation is only applicable to the asthma population. Participants over the age of 50 will be required to provide proof of COVID-19 vaccination before being eligible to participate.
Section 5.1.2 Inclusion Criteria: Part C (Participants with Asthma), number 3	Inclusion of British Thoracic Society/ Scottish Intercollegiate Guidelines Network (BTS/SIGN), for physician confirmed diagnosis of asthma	The diagnosis of asthma in the UK is likely to be according to BTS/SIGN or GINA guidelines.
Section 5.1.2 Inclusion Criteria: Part C (Participants with Asthma)	Removal of the requirement for bronchodilator reversibility as an inclusion criterion for SABA only requiring population	In the mild asthma SABA only requiring population the ability to demonstrate bronchodilator reversibility is highly variable. Therefore, participants in this group may now be permitted to be included (without demonstration of bronchodilator reversibility) if they have a physician confirmed diagnosis of asthma, at least 6 months before screening.

Section # and Name	Description of Change	Brief Rationale
Section 5.1.2 Inclusion Criteria: Part C (Participants with Asthma), number 5	Updated 'SABA only' treatment to include treatment with 'intermittent' ICS/LABA	Population treatment requirements updated in line with updated treatment guidelines.
Section 6.1 Study Intervention(s) administered, Cohort 2	Removal of 2000 mcg: four capsules, single dose	This dose level was included in the planned study intervention(s) table in error. This dose was not one of the planned study intervention(s) dose levels.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Updated access to unblinded data from complete cohorts to include safety endpoints	To allow better interpretation of both safety and PK data following the completion of each cohort, to help the design of future studies.
Section 8.3.1 Plasma Sample Collection	Reduction in the number of plasma PK samples that may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor.	One additional sample at 15 mins has been added to the study since the last protocol amendment.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomised double-blind, placebo controlled, single ascending and repeat dose, First Time in Human study in healthy participants and stable asthmatics to assess safety, tolerability and pharmacokinetics of GSK3923868 inhalation powder

Brief Title: Safety, tolerability and pharmacokinetics of GSK3923868 inhalation powder in healthy participants and stable asthmatics.

Rationale: This is a first time in human (FTIH) study designed to evaluate the safety, tolerability and pharmacokinetic (PK) profile of single and repeat doses of GSK3923868 inhalation powder in both healthy participants and asthmatics. The study will use the Monodose RS01 inhaler for drug delivery. This study aims to provide evaluate the safety and tolerability profile of the molecule and will obtain preliminary information regarding PK to support future clinical development.

Phosphatidylinositol 4-kinase beta (PI4KB) is a human intracellular lipid kinase that catalyses the formation of phosphatidylinositol-4-phosphate (PI4P), a key component of the Golgi and trans-Golgi network membranes and regulator of trafficking to and from the Golgi body.

PI4KB is host factor required for the replication of multiple picornaviruses, including human rhinovirus (HRV). Following cell entry, HRV proteins produced by translation of viral RNA recruit PI4KB to the Golgi membrane, where increased synthesis of PI4P drives membrane cholesterol enrichment. The role of PI4KB is crucial for viral polyprotein processing and for the formation of replication organelles where viral replication takes place.

HRV are small, non-enveloped, positive sense RNA viruses belonging to the family *Picornaviridae* and genus *Enterovirus*. The characteristic clinical manifestation of HRV infection is the common cold, for which HRV is responsible for approximately 50% of cases, though during seasonal peaks in autumn and spring, incidence can be up to 80%.

The symptoms related to HRV infection are generally limited to the upper respiratory tract (e.g. rhinorrhoea, sore throat, sneezing) and of minimal clinical concern. However, in the context of chronic respiratory diseases, such as COPD and asthma, HRV has been shown to induce lower respiratory tract symptoms (e.g. cough, wheeze and shortness of breath) and is the predominant viral stimulus leading to exacerbations. Furthermore, HRV infection may increase host susceptibility to secondary bacterial infection through upregulation of cell surface receptors, disruption of normal epithelial barrier function and through impairment of macrophage response following exposure to bacterial toll-like receptors.

Preclinical data support the use of GSK3923868 in the treatment of HRV infection. In air-liquid interface cultures of fully differentiated human bronchial epithelial cells, GSK3923868 has been shown to exhibit potent and slowly reversible inhibition of HRV replication (t1/2 ~ 50 h via washout protocol). *In vitro* data also indicates that

GSK3923868 is a potent inhibitor of viral replication in a broad number of HRV strains from both major and minor groups (HRV-A and HRV-B species, IC_{50} range 0.3 to 3.9 nM respectively). In other experiments, HRV-C species have also been shown to be sensitive to PI4KB inhibition.

There are currently no licensed treatments or vaccines for HRV, with previous treatments generally targeting virus-specific factors including capsid binding and cell entry or inhibition of viral enzymes (e.g. 3C protease) necessary for viral genome processing and replication. The failure to develop an effective treatment has been attributed to the antigenic diversity of HRV which has over 160 serotypes and also the rapid emergence of drug resistance. As PI4KB inhibition is a host target, it is expected to exhibit a comparably higher barrier to resistance.

As a selective and potent inhibitor of PI4KB, GSK3923868 has the potential to inhibit viral replication whilst permitting normal immune mediated clearance of the virus. This could lead to reduced symptoms, prevention of HRV driven exacerbations and prevention of secondary bacterial infections.

Objectives and Endpoints: Parts A and B (Healthy participants)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3923868 following single and repeat inhaled administration in healthy participants.	• Adverse events (AEs) and serious adverse events (SAEs). • Clinically significant laboratory values, vital signs,12-lead electrocardiogram (ECG) and spirometry measurements up to Day 2 of the final treatment period in Part A, and Day 18 in Part B.
Secondary	
• To evaluate the plasma pharmacokinetics of GSK3923868 following single and repeat inhaled administration in healthy participants.	Derived pharmacokinetic parameters as data permit, including (but not limited to): Single dose (Part A, Cohorts 1 & 2): • Area under the plasma GSK3923868 concentration versus time curve from time zero to last quantifiable concentration (AUC(0-t)) and from time zero to infinity (AUC(0-∞)) (if determined). • Maximum observed GSK3923868 plasma concentration (Cmax). • Time to maximum observed plasma drug concentration (Tmax). Repeated dose (Part B, Cohorts 3 & 4): • AUC(0-τ) on Day 1 and Day 14 (τ=24h for once a day dosing regimen) (if determined). • Cmax and Tmax on Day 1 and Day 14.
CCI [redacted]	

Objectives	Endpoints
CCI	[redacted]

Objectives and Endpoints: Part C (Participants with Asthma)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3923868 following repeat inhaled administration in participants with asthma.	• AE and SAEs • Clinically significant laboratory values, vital signs, 12-lead ECG and spirometry measurements up to Day 8.
Secondary	
• To evaluate the plasma pharmacokinetics of GSK3923868 following repeat inhaled administration in participants with asthma.	• AUC(0-τ) on Day 1 and Day 7 (τ=24h for once a day dosing regimen) (if determined). • Cmax and Tmax on Day 1 and Day 7.

Overall Design:

This is a 3-part, randomised, double-blind, placebo controlled, study designed to assess the safety, tolerability and PK of GSK3923868 administered as an inhalation powder blend (GSK3923868 capsules for inhalation) via the Monodose inhaler in healthy participants (Parts A and B) and in participants with asthma (Part C).

In all parts, participants who meet the criteria for study entry will be randomised to receive GSK3923868 (active) or placebo before study intervention administration on Day 1.

As this study represents the first administration of GSK3923868 to humans, sentinel dosing will be utilised for each increasing dose level in Part A (if the selected dose level is below the previous dose level, sentinel dosing may still be applied) and before initiating full cohort repeat dosing in Part B. Each sentinel sub-cohort will consist of two participants receiving GSK3923868 or placebo (i.e. one will receive active and one will receive placebo). The decision to dose the remaining participants in each cohort will be based on the review of safety and tolerability data (i.e. AE/SAE, clinical safety laboratory assessments, vital signs, 12-lead safety ECGs and spirometry) from the sentinel sub-cohort by the Principal Investigator (PI) or appropriately qualified delegate, in consultation with the Medical Monitor. For Part A this will include data up to 24 hours post-dose and in Part B will include all data up Day 14, 24 hours.

In addition, a Dose Escalation Committee (DEC) will be responsible for the review of emerging safety, tolerability and plasma PK results to determine the progression of single ascending dose levels in each treatment period in Part A and the progression to repeat dose levels in Parts B and C.

Brief Summary:

For Part A, sufficient healthy adult participants will be screened to ensure a total of 24 participants are randomised in Cohorts 1 and 2 with the aim to achieve approximately 24 completed. Cohorts 1 and 2 will each consist of 12 healthy participants receiving study intervention in treatment periods 1 to 3 and 4 to 6 (9 active and 3 placebo per period), respectively.

In Part B, sufficient healthy adult participants will be screened to ensure 8 healthy participants are randomised to each of the two cohorts, with the aim to achieve approximately 8 completed in each cohort. A total of 16 healthy participants will be randomised in Part B to achieve 16 completers, 12 on active and 4 on placebo (6 active and 2 placebo in each of Cohorts 3 and 4).

For Part C, sufficient participants with asthma will be screened to ensure 16 participants are randomised, with the aim to achieve 16 completers, 12 on active and 4 on placebo.

If participants prematurely discontinue the study, they will be replaced at the discretion of the sponsor Medical Monitor in consultation with the Principal Investigator. In Part A, the replacement participant will be assigned to the same treatment sequence and may start the treatment period where the last participant prematurely discontinued. In Parts B and C participants will be assigned to same treatment as the last participant prematurely discontinued.

Each participant may only be randomised to one cohort and may only participate in one part of the study.

Number of Participants:

A total of approximately 56 participants will be enrolled across the entire study, comprising of 40 healthy participants (in Parts A and B) and 16 participants with asthma (in Part C).

Note: "Enrolled" means a participant's, agreement to participate in the clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

The total duration of study participation in each part of the study is summarised in the table below:

Part	Screening	Treatment Period	Washout Period	Follow-Up	Total Duration
A	Up to 30 days before the first dose.	Cohort 1 will be comprised of three treatment periods (3days each) with a follow up phone call at 48 hours after each dose.	Will be at least 10 days between doses for each participant.	Between 7 to 14 days following the final dose.	Approx. 11 weeks
A		Cohort 2 will be comprised of three treatment periods (4 days each).			
B		Each participant will receive up to 14 days of treatment with additional observation up to 96 hours after their final dose.	N/A		Approx. 9 weeks
C		Each participant will receive up to 7 days of treatment.	N/A		Approx. 8 weeks

Each participant may only be randomised to one cohort and may only participate in one part of the study.

Part A: Single Dose Escalation in Healthy Participants (Crossover)

In Part A, single ascending doses of GSK3923868 will be assessed in two sequential crossover cohorts (Cohorts 1 and 2) of healthy participants, each with up to three treatment periods. In each cohort, 12 participants will be randomised to one of four treatment sequences. Across the three treatment periods, 9 participants will receive placebo in one of the periods, whereas 3 participants will receive an active dose in all periods (see below table for further details).

Treatment Period	Cohort 1				Cohort 2			
	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)
1	A	A	A	P	-			
2	P	A	A	A	-			
3	A	P	A	A	-			
4	-				P	A	A	A
5	-				A	P	A	A
6	-				A	A	P	A

The planned dose levels in each treatment period outlined in Section 4.3.1 will be conducted only if it is supported by safety, tolerability and plasma PK results (from a

minimum of 5 participants on active treatment) from the preceding dose level(s) and may be modified based on emerging data.

A minimum of 10 days washout is required between each treatment period.

Part B: Repeat Dose in Healthy Participants (Parallel Group)

Part B will assess repeat doses of GSK3923868 for 14 days across two parallel cohorts (Cohorts 3 and 4) of 8 healthy participants (total 16 participants in Part B). The dose selected for Part B will be based on the full review of safety, tolerability and plasma PK data in Part A. The dose for Part B will not exceed the top dose used in Part A. In addition, the predicted steady state systemic exposure in Part B will not intentionally exceed the predetermined systemic exposure stopping criteria (Section 6.5). Both cohorts in Part B are proposed to receive the same dose.

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[redacted]

Part C: Repeat Dose in Participants with Asthma (Parallel Group)

In Part C, further repeat dosing of GSK3923868 for 7 days will be assessed in a single parallel cohort (Cohort 5) of 16 participants with stable asthma. The dose for Part C will be based on the review of safety, tolerability and plasma PK data in Part B up to Day 14, 24 hours (from a minimum of 10 participants on active treatment). The dose level in Part C will not exceed the dose used in Part B. CCI [redacted].

Participants in Part C will be recruited based on their asthma severity, such that 8 participants will be mild or intermittent asthmatics requiring only treatment with short-acting beta agonist (SABA) and/or intermittent inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination and 8 participants will have moderate asthma requiring regular treatment with ICS or ICS/LABA. Randomisation will be stratified to ensure 6 participants using SABA and/or intermittent ICS/LABA and 6 participants taking regular ICS or ICS/LABA will be on active treatment.

Data Monitoring/ Other Committee: No Data Monitoring Committee. A Dose Escalation Committee: Yes

A dose escalation committee (DEC) will be responsible for on-going monitoring during the study.

As this study represents the first administration of GSK3923868 to humans, a dose escalation committee (DEC) will be responsible for reviewing all available safety, tolerability and PK data to determine progressing dose levels in Part A and before initiating repeat dosing in Parts B and C.

The DEC will at a minimum consist of the following:

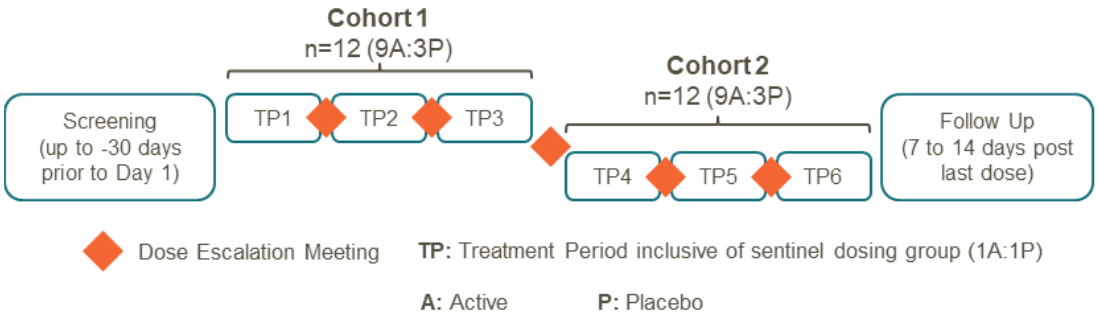
- Principal Investigator (or suitably qualified delegate)
- From GSK:
    - Medical Monitor
    - Clinical Pharmacology, Modelling and Simulation representative
    - Safety and Medical Governance representative
    - Statistician

To minimise the risk of unblinding during DEC meetings, individual PK data will be scrambled such that the blind is maintained. Summary statistics will also be provided for plasma PK parameters (Cmax and AUC). The data may be unblinded should a safety concern arise during the blinded review.

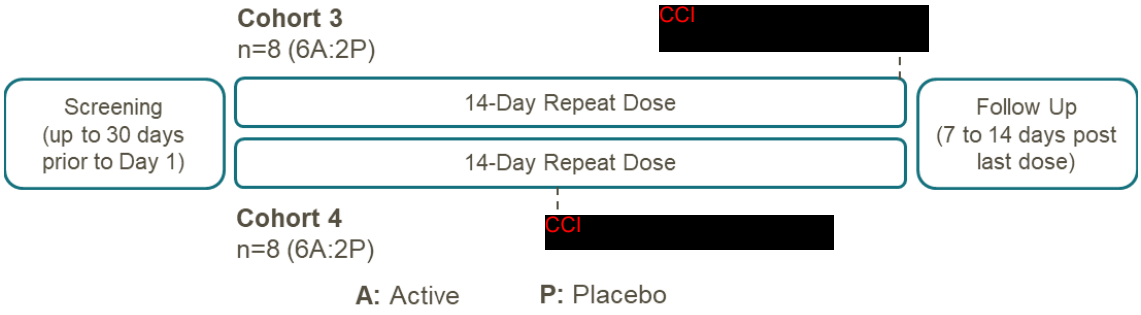
Further details on the dose escalation process, dose modification and escalation stopping criteria and the DEC are outlined in the protocol and Dose Escalation Plan.

1.2. Schema

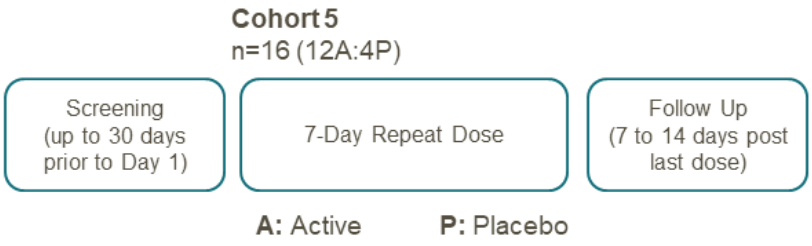
Part A: Single Ascending Dose | Healthy Participants



Part B: Repeat Dose | Healthy Participants



Part C: Repeat Dose | Participants with Asthma



1.3. Schedule of Activities (SoA)

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.
- The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

Parts A, B and C: Screening and Follow Up

Procedure	Screening (up to -30 days before Day 1)	Follow Up (7 to 14 days post last dose)
Outpatient Visit	X	
Telephone Call		X
Informed Consent	X	
Review Inclusion and Exclusion Criteria	X	
Demography	X	
Medical History (includes substance usage, smoking status and medication history)	X	
Full Physical Examination (includes height, weight and BMI)	X	
AE Review		X
SAE Review	X	X
Concomitant Medication Review	X	X
Spirometry[1]	X	
Peak Expiratory Flow (PEF) Training[2]	X	
PEF[2]	X	
Vital Signs[3]	X	
12-Lead Safety ECG[4]	X	
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Safety Laboratory Assessment[5]	X	
HIV, Hepatitis B and C Screening	X	
COVID-19 Test[7]	X	
β-hCG Pregnancy/Estradiol/FSH Tests	X	
Alcohol and Smoking Breath Test	X	
Urine Drug Screen	X	

1. Measure forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) in triplicate.
2. For Part C only – Triplicate measurements and training of the participant in how to take measurements will occur at screening.
3. Includes systolic and diastolic blood pressure, heart rate, respiration rate and tympanic temperature.
4. Screening ECG to be performed in triplicate.

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6. Clinical Chemistry, Haematology, Coagulation and Urinalysis.
7. To be performed according to local site procedures. Additional ad hoc testing may be implemented based on local site procedures.

Part A: Single Ascending Dose | Healthy Participants (Cohort 1)

Procedure	Treatment Periods 1 to 3														
	Day -1	Day 1												Day 2 (D1+24h)	Day 3 (D1+ 48h)
		Pre-dose	0	5m	30m	45m	1h	2h	4h	6h	8h	12h	16h		
Admission to Clinical Unit	X														
Discharge														X	
Phone Call															X
Brief Physical Examination	X													X	
Inhaler Training[1]	X														
Alcohol and Smoking Breath Test	X														
Urine Drug Screen	X														
COVID-19 Test[2]	X													X	
Urine Pregnancy Test	X														
Randomisation		X													
Treatment Administration[3]			X												
AE Review			◄	———	———	———	———	———	———	———	———	———	———	———	►
SAE Review	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Concomitant Medication Review			◄	———	———	———	———	———	———	———	———	———	———	———	►
Spirometry (FEV1 and FVC)[4]		X					X								
Vital Signs[5]	X	X			X		X		X			X		X	
12-Lead Safety ECG[6]	X	X		X	X		X		X			X		X	
Telemetry[7]		◄	———	———	———	———	———	———	———	———	►				
CCI [redacted]															
Laboratory Safety Assessment[9]	X													X	
PK Blood Sample		X		X	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]															

Footnotes to Part A: Single Ascending Dose | Healthy Participants (Cohort 1)

1. Day -1 inhaler training may be performed on Day 1 if needed and before administration of the first dose. Additional training may be provided as needed and according to Investigator discretion.
2. To be performed according to local site procedures. Additional ad hoc testing may be implemented based on local site procedures.
3. No meals from 2 hours before dosing until 2 hours post dose.
4. Perform in triplicate and includes FEV1 and FVC.
5. Includes systolic and diastolic blood pressure, heart rate, respiration rate and tympanic temperature.
6. On Day 1 pre-dose of each treatment period, triplicate ECG measurements will be collected, and the mean values will be used to calculate baseline. At all other time points single ECGs will be taken.
7. Cardiac telemetry to start approximately 1-hour pre-dose and continuously until 6 hours post dose.

CCI [redacted]

9. Clinical Chemistry and Haematology only.

CCI [redacted]

Part A: Single Ascending Dose | Healthy Participants (Cohort 2)

Procedure	Treatment Periods 4 to 6														
	Day -1	Day 1												Day 2 (D1+24h)	Day 3 (D1+ 48h)
		Pre-dose	0	5m	30m	45m	1h	2h	4h	6h	8h	12h	16h		
Admission to Clinical Unit	X														
Discharge															X
Phone Call															
Brief Physical Examination	X													X	
Inhaler Training[1]	X														
Alcohol and Smoking Breath Test	X														
Urine Drug Screen	X														
COVID-19 Test[2]	X														X
Urine Pregnancy Test	X														
Randomisation		X													
Treatment Administration[3]			X												
AE Review			◄	———	———	———	———	———	———	———	———	———	———	———	►
SAE Review	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Concomitant Medication Review			◄	———	———	———	———	———	———	———	———	———	———	———	►
Spirometry (FEV1 and FVC)[4]		X					X								
Vital Signs[5]	X	X			X		X		X			X		X	
12-Lead Safety ECG[6]	X	X		X	X		X		X			X		X	
Telemetry[7]		◄	———	———	———	———	———	———	———	———	►				
CCI															
Laboratory Safety Assessment[9]	X													X	
PK Blood Sample		X		X	X	X	X	X	X	X	X	X	X	X	X
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Footnotes to Part A: Single Ascending Dose | Healthy Participants (Cohort 2)

1. Day -1 inhaler training may be performed on Day 1 if needed and before administration of the first dose. Additional training may be provided as needed and according to Investigator discretion.
2. To be performed according to local site procedures. Additional ad hoc testing may be implemented based on local site procedures.
3. No meals from 2 hours before dosing until 2 hours post dose.
4. Perform in triplicate and includes FEV1 and FVC.
5. Includes systolic and diastolic blood pressure, heart rate, respiration rate and tympanic temperature.
6. On Day 1 pre-dose of each treatment period, triplicate ECG measurements will be collected, and the mean values will be used to calculate baseline. At all other time points single ECGs will be taken.
7. Cardiac telemetry to start approximately 1-hour pre-dose and continuously until 6 hours post dose.

CCI [redacted]

9. Clinical Chemistry and Haematology only.

CCI [redacted]

Part B: Repeat Dose | Healthy Participants (Cohorts 3 and 4)

Procedure	Inpatient Period																		
	D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15 (D14+ 24h)	D16 (D14+ 48h)	D17 (D14+ 72h)	D18 (D14+ 96h)
Admission to Clinical Unit	X																		
Discharge																			X
Brief Physical Examination	X		X													X			X
Inhaler Training[1]	X																		
Alcohol and Smoking Breath Test	X																		
Urine Drug Screen	X																		
COVID-19 Test[2]	X				X								X						X
Urine Pregnancy Test	X																		
Randomisation		X																	
Treatment Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X				
AE Review		←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
SAE Review	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant Medication Review		←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Spirometry (FEV1 & FVC)		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X			
Vital Signs[4]	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X			X
12-Lead Safety ECG[6]	X	X	X		X		X		X		X		X		X	X			X
Telemetry		X[7]																	

Procedure	Inpatient Period																		
	D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15 (D14+ 24h)	D16 (D14+ 48h)	D17 (D14+ 72h)	D18 (D14+ 96h)
CCI																			
Laboratory Safety Assessment[9]	X		X[5]		X[5]		X[5]		X[5]		X[5]		X[5]		X[5]	X			X
PK Blood Sample		X[10, 16]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5, 11]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[10, 16]	X	X	X	X
CCI																			

Footnotes to Part B: Repeat Dose Repeat Dose | Healthy Participants (Cohorts 3 and 4)

1. Day -1 inhaler training may be performed on Day 1 if needed and before administration of the first dose. Additional training may be provided as needed and according to Investigator discretion.
2. To be performed according to local site procedures. Day 4 to 6 test is required for Cohort 4 only ahead of bronchoscopy on Day 7. Day 12 to 14 test is required for Cohort 3 only ahead of bronchoscopy on Day 15. Additional ad hoc testing may be implemented based on local site procedures.
3. Predose and 1-hour post-dose only.
4. Includes systolic and diastolic blood pressure, heart rate, respiration rate and tympanic temperature.
5. Predose.
6. On treatment days ECGs will be collected at predose and 6-hours post-dose. On Day 1 predose, triplicate measurements will be collected, and the mean values will be used to calculate baseline. At all other times single ECGs can be taken.
7. Cardiac telemetry to start approximately 1-hour pre-dose and continuously until 6 hours post dose.

CCI [redacted]

9. Clinical Chemistry and Haematology at all visits. Coagulation will be assessed on Day 4 for both cohorts.
10. At pre-dose, 5 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h and 16 h.

CCI [redacted]

16. At 15 min.

Part C: Repeat Dose | Asthma (Cohort 5)

Procedure	Inpatient Period								
	D-1	D1	D2	D3	D4	D5	D6	D7	D8 (D7+ 24h)
Admission to Clinical Unit	X								
Discharge									X
Review Inclusion and Exclusion Criteria	X								
Brief Physical Examination	X		X						X
Inhaler Training[1]	X								
Alcohol and Smoking Breath Test	X								
Urine Drug Screen	X								
COVID-19 Test[2]	X								X
Urine Pregnancy Test	X								
Randomisation		X							
Treatment Administration		X	X	X	X	X	X	X	
AE Review		←	—	—	—	—	—	—	→
SAE Review	←	—	—	—	—	—	—	—	→
Concomitant Medication Review		←	—	—	—	—	—	—	→
Spirometry (FEV1 & FVC)		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X
PEF[4]	X[5]	X	X	X	X	X	X	X	X
Vital Signs[6]	X	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X
12-Lead Safety ECG[8]	X	X	X		X		X	X	X
Telemetry		X[9]							
Laboratory Safety Assessment[10]	X		X[7]		X[7]		X[7]		X
PK Blood Sample		X[11]	X[7]	X[7]	X[7]	X[7]	X[7]	X[11]	X

Footnotes to Part C: Repeat Dose | Asthma (Cohort 5)

1. Day -1 inhaler training may be performed on Day 1 if needed and before administration of the first dose. Additional training may be provided as needed and according to Investigator discretion.
2. To be performed according to local site procedures. Additional ad hoc testing may be implemented based on local site procedures.
3. Predose and 30 min only.
4. PEF measurements will be taken in triplicate twice each day (once in morning upon waking and once in the evening before bedtime) from Day -1 evening until discharge on Day 8. Clinical site staff will complete and record the PEF measurements at each time point.
5. Provide PEF device refresher training if necessary.
6. Includes systolic and diastolic blood pressure, heart rate, respiration rate and tympanic temperature.
7. Predose only
8. On treatment days ECGs will be collected at predose and 6-hours post-dose. On Day 1 predose, triplicate measurements will be collected, and the mean values will be used to calculate baseline. At all other times single ECGs can be taken.
9. Cardiac telemetry to start approximately 1-hour pre-dose and continuously until 6 hours post dose.
10. Clinical Chemistry and Haematology only.
11. At pre-dose, 5 min, 15 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h and 16 h

2. INTRODUCTION

Phosphatidylinositol 4-kinase beta (PI4KB) is a human intracellular lipid kinase that catalyses the formation of phosphatidylinositol-4-phosphate (PI4P), a key component of the Golgi and trans-Golgi network membranes and regulator of trafficking to and from the Golgi body.

PI4KB is a host factor required for the replication of multiple picornaviruses, including human rhinovirus (HRV). Following cell entry, HRV proteins produced by translation of viral RNA recruit PI4KB to the Golgi membrane, where increased synthesis of PI4P drives membrane cholesterol enrichment. The role of PI4KB is crucial for viral polyprotein processing and for the formation of replication organelles where viral replication takes place [Hsu, 2010; Altan-Bonnet, 2012; Roulin, 2014].

GSK3923868 is a selective and potent inhibitor of PI4KB being developed for respiratory disease and specifically the treatment of rhinovirus associated exacerbations of chronic obstructive pulmonary disease (COPD) and asthma. GSK3923868 is not an immunomodulatory drug.

2.1. Study Rationale

This is a first time in human (FTIH) study designed to evaluate the safety, tolerability and pharmacokinetic (PK) profile of single and repeat inhaled doses of GSK3923868 in both healthy participants and asthmatics. The study will use the Monodose RS01 inhaler for drug delivery. This study aims to evaluate the safety and tolerability profile of the molecule and will also obtain preliminary information regarding PK to support future clinical development.

2.2. Background

HRV are small, non-enveloped, positive sense RNA viruses belonging to the family *Picornaviridae* and genus *Enterovirus*. The characteristic clinical manifestation of HRV infection is the common cold, for which HRV is responsible for approximately 50% of cases, though during seasonal peaks in autumn and spring, incidence can be up to 80% [Turner, 2007].

The symptoms related to HRV infection are generally limited to the upper respiratory tract (e.g. rhinorrhoea, sore throat, sneezing) and of minimal clinical concern. However, in the context of chronic respiratory diseases, such as COPD and asthma, HRV has been shown to induce lower respiratory tract symptoms (e.g. cough, wheeze and shortness of breath) and is the predominant viral stimulus leading to exacerbations [Hershenson, 2013]. Furthermore, HRV infection may increase host susceptibility to secondary bacterial infection by upregulation of cell surface receptors, disruption of normal epithelial barrier function and through impairment of macrophage response following exposure to bacterial toll-like receptors [Jacobs, 2013].

Preclinical data support the use of GSK3923868 in the treatment of HRV infection. In air-liquid interface cultures of fully differentiated human bronchial epithelial cells, GSK3923868 has been shown to exhibit potent and slowly reversible inhibition of HRV

replication (t1/2 ~ 50 h via washout protocol). *In vitro* data also indicates that GSK3923868 is a potent inhibitor of viral replication in a broad number of HRV strains from both major and minor groups (HRV-A and HRV-B species, IC_{50} range 0.3 to 3.9 nM). In other experiments, HRV-C species have also been shown to be sensitive to PI4KB inhibition [Mello, 2014].

There are currently no licensed treatments or vaccines for HRV, with previous treatments generally targeting virus-specific factors including capsid binding and cell entry or inhibition of viral enzymes (e.g. 3C protease) necessary for viral genome processing and replication. The failure to develop an effective treatment has been attributed to the antigenic diversity of HRV which has over 160 serotypes and also the rapid emergence of drug resistance [Casanova, 2018]. As PI4KB inhibition is a host target, it is expected to exhibit a comparably higher barrier to resistance.

As a selective and potent inhibitor of PI4KB, GSK3923868 has the potential to inhibit viral replication whilst permitting normal immune mediated clearance of the virus. This could lead to reduced symptoms, prevention of HRV driven exacerbations and prevention of secondary bacterial infections.

A detailed description of the chemistry, preclinical pharmacology, efficacy and safety of GSK3923868 is provided in the Investigator's Brochure [GSK Document Number 2020N427621_00].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3923868 may be found in the Investigator's Brochure [GSK Document Number 2020N427621_00].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention [GSK3923868]		
Bronchospasm	Can potentially occur with any inhaled treatment.	Inclusion/Exclusion criteria: In Parts A and B healthy participants with an FEV1 and an FVC < 80% of predicted normal value will be excluded. In Part C only participants with mild to moderate asthmatics with a pre-bronchodilator FEV1 > 65% of predicted normal value will be recruited. Monitoring: All doses of study treatment will be administered in the clinical pharmacology unit in the presence of clinical staff. Spirometry will be conducted pre and post dose to monitor participants. Management: Treatment with a short-acting inhaled bronchodilator will be available. If bronchospasm occurs GSK3923868 will be discontinued immediately. The participant will be assessed and, if necessary, further therapy will be given as deemed appropriate by the Investigator or the attending physician. Participants will be withdrawn from the study if bronchospasm occurs.
Respiratory tract irritancy	In rats dosed for 4 weeks by inhaled administration, microscopic findings were noted in the lungs and bronchi, with minimal degeneration/regeneration of the epithelium at	Appropriate safety margin: Maximum clinical exposure at 3 mg are expected to be below the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	the bronchioloalveolar junction at 2060 µg/kg/day. In addition, an increased incidence of inflammatory cell infiltrate (minimal or slight severity), composed predominantly of granulocytes, of the peribronchiolar/perivascular interstitium was also seen at 2060 µg/kg/day. Minimal or slight inflammatory cell infiltrate was seen at a higher than control incidence in females given 2060 µg/kg/day only. However, no microscopic findings in dog IH and rat IV studies.	NOAEL exposure margins (AUC: 15-fold; Cmax: 5-fold; lung deposition: 5-fold). Monitoring: respiratory AEs will be monitored and spirometry will be conducted pre- and post-dosing in all three parts of the study. In addition, peak expiratory flow (PEF) monitoring will be implemented for asthmatics in Part C. Sentinel dosing will be used at each dose escalation (Part A), and also for one of the repeat dose cohorts (Part B). Escalation will only proceed after a blinded review of safety, tolerability and plasma PK obtained in at least 5 participants on active treatment at the prior dose level.
Study Procedures		
Spirometry assessments	Shortness of breath, coughing, light headedness or fainting, and/or chest tightness during the spirometry assessments.	As specified in the informed consent form for this study, if any of these symptoms should occur, the participant will receive appropriate medical treatment.
CCI [redacted]		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	

2.3.2. Benefit Assessment

No clinical benefit is expected for the healthy participants or asthma patients enrolled in this FTIH study, as evidence for the potential of clinical benefits of GSK3923868 is yet to be determined. Furthermore, clinical benefit would not be expected in participants not experiencing a human rhinovirus infection.

However, participants may benefit in the knowledge that they are contributing to the process of developing new therapies in an area of unmet need. Participants may also benefit from the thorough medical assessments they receive during the course of the study.

2.3.3. Overall Benefit: Risk Conclusion

This study will be conducted in a fully equipped clinical pharmacology unit with access to hospital emergency facilities. Considering the measures taken to minimise the potential risks associated with participation in this study, the enrolment of healthy participants and stable asthma patients is considered justified by the anticipated benefits that may be afforded to participants with COPD and Asthma in the future.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives and Endpoints: Parts A and B (Healthy Participants)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3923868 following single and repeat inhaled administration in healthy participants.	• Adverse events (AEs) and serious adverse events (SAEs). • Clinically significant laboratory values, vital signs,12-lead electrocardiogram (ECG) and spirometry measurements up to Day 2 of the final treatment period in Part A, and Day 18 in Part B.
Secondary	
• To evaluate the plasma pharmacokinetics of GSK3923868 following single and repeat inhaled administration in healthy participants.	Derived pharmacokinetic parameters as data permit, including (but not limited to): Single dose (Part A, Cohorts 1 & 2): • Area under the plasma GSK3923868 concentration versus time curve from time zero to last quantifiable concentration (AUC(0-t)) and from time zero to infinity (AUC(0-∞)) (if determined). • Maximum observed GSK3923868 plasma concentration (Cmax). • Time to maximum observed plasma drug concentration (Tmax). Repeated dose (Part B, Cohorts 3 & 4): • AUC(0-τ) on Day 1 and Day 14 (τ=24h for once a day dosing regimen) (if determined). • Cmax and Tmax on Day 1 and Day 14.
CCI [redacted]	

Objectives	Endpoints
CCI	[redacted]

3.2. Objectives and Endpoints: Part C (Participants with Asthma)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of GSK3923868 following repeat inhaled administration in participants with asthma.	• AE and SAEs • Clinically significant laboratory values, vital signs, 12-lead ECG and spirometry measurements up to Day 8.
Secondary	
• To evaluate the plasma pharmacokinetics of GSK3923868 following repeat inhaled administration in participants with asthma.	• AUC(0-τ) on Day 1 and Day 7 (τ=24h for once a day dosing regimen) (if determined). • Cmax and Tmax on Day 1 and Day 7.

4. STUDY DESIGN

4.1. Overall Design

This is a 3-part, randomised, double-blind, placebo controlled, study designed to assess the safety, tolerability and PK of GSK3923868 administered as an inhalation powder blend (GSK3923868 capsules for inhalation) via Monodose inhaler in healthy participants (Parts A and B) and in participants with asthma (Part C).

In all parts, participants who meet the criteria for study entry will be randomised to receive GSK3923868 (active) or placebo before study intervention administration on Day 1.

As this study represents the first administration of GSK3923868 to humans, sentinel dosing will be utilised for each increasing dose level in Part A (if the selected dose level is below the previous dose level, sentinel dosing may still be applied) and before initiating full cohort repeat dosing in Part B. Each sentinel sub-cohort will consist of two participants receiving GSK3923868 or placebo (i.e. one will receive active and one will receive placebo). The decision to dose the remaining participants in each cohort will be based on the review of safety and tolerability data (i.e. AE/SAE, clinical safety laboratory assessments, vital signs, 12-lead safety ECGs and spirometry) from the sentinel sub-cohort by the Principal Investigator (PI) or appropriately qualified delegate, in consultation with the Medical Monitor. For Part A this will include data up to 24 hours post-dose and in Part B will include all data up Day 14, 24 hours.

In addition, a Dose Escalation Committee (DEC) will be responsible for the review of emerging safety, tolerability and plasma PK results to determine the progression of single ascending dose levels in each treatment period in Part A and the progression to repeat dose levels in Parts B and C. Dose modification and escalation stopping criteria are outlined in Section 6.5 and the DEC committee structure is outlined in Section 10.1.5. Further information on the dose escalation process is outlined in the Dose Escalation Plan.

The total duration of study participation in each part of the study is summarised in Table 1.

Table 1 Summary of study duration for study Parts A, B and C

<table>
<tr><th>Part</th><th>Screening</th><th>Treatment Period</th><th>Washout Period</th><th>Follow-Up</th><th>Total Duration</th></tr>
<tr><td>A</td><td rowspan="4">Up to 30 days before the first dose.</td><td>Cohort 1 will be comprised of three treatment periods (3 days each) with a follow up phone call at 48 hours after each dose.</td><td rowspan="2">Will be at least 10 days between doses for each participant.</td><td rowspan="4">Between 7 to 14 days following the final dose.</td><td rowspan="2">Approx. 11 weeks</td></tr>
<tr><td>A</td><td>Cohort 2 will be comprised of three treatment periods (4 days each).</td></tr>
<tr><td>B</td><td>Each participant will receive up to 14 days of treatment with additional observation up to 96 hours after their final dose.</td><td>N/A</td><td>Approx. 9 weeks</td></tr>
<tr><td>C</td><td>Each participant will receive up to 7 days of treatment.</td><td>N/A</td><td>Approx. 8 weeks</td></tr>
</table>

Each participant may only be randomised to one cohort and may only participate in one part of the study.

Part A: Single Dose Escalation in Healthy Participants (Crossover)

In Part A, single ascending doses of GSK3923868 will be assessed in two sequential crossover cohorts (Cohorts 1 and 2) of healthy participants, each with up to three treatment periods. In each cohort, 12 participants will be randomised to one of four treatment sequences. Across the three treatment periods, 9 participants will receive placebo in one of the periods, whereas 3 participants will receive an active dose in all periods (see Table 2 for further details).

Table 2 Example treatment sequence randomisation for Part A

Treatment Period	Cohort 1				Cohort 2			
	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)
1	A	A	A	P	-			
2	P	A	A	A	-			
3	A	P	A	A	-			
4	-				P	A	A	A
5	-				A	P	A	A
6	-				A	A	P	A

The planned dose levels in each treatment period outlined in Section 4.3.1 will be conducted only if it is supported by safety, tolerability and plasma PK results (from a minimum of 5 participants on active treatment) from the preceding dose level(s) and may be modified based on emerging data.

A minimum of 10 days washout is required between each treatment period.

Part B: Repeat Dose in Healthy Participants (Parallel Group)

Part B will assess repeat doses of GSK3923868 for 14 days across two parallel cohorts (Cohorts 3 and 4) of 8 healthy participants (total 16 participants in Part B). The dose selected for Part B will be based on the full review of safety, tolerability and plasma PK data in Part A. The dose for Part B will not exceed the top dose used in Part A. In addition, the predicted steady state systemic exposure in Part B will not intentionally exceed the predetermined systemic exposure stopping criteria (Section 6.5). Both cohorts in Part B are proposed to receive the same dose.

CCI [redacted]

Part C: Repeat Dose in Participants with Asthma (Parallel Group)

In Part C, further repeat dosing of GSK3923868 for 7 days will be assessed in a single parallel cohort (Cohort 5) of 16 participants with stable asthma. The dose for Part C will be based on the review of safety, tolerability and plasma PK data in Part B up to Day 14, 24 hours (from a minimum of 10 participants on active treatment). The dose level in Part C will not exceed the dose used in Part B. CCI [redacted]

Participants in Part C will be recruited based on their asthma severity, such that 8 participants will be mild or intermittent asthmatics requiring only treatment with short-acting beta agonist (SABA) and/or intermittent inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination and 8 participants will have moderate asthma requiring regular treatment with ICS or ICS/LABA. Randomisation will be stratified to ensure 6 participants using intermittent SABA or intermittent ICS/LABA and 6 participants taking regular ICS or ICS/LABA will be on active treatment.

4.2. Scientific Rationale for Study Design

This study has been designed in accordance with regulatory guidance for the conduct of First Time in Human (FTIH) studies. Preclinical assessments of GSK3923868 contribute to the number and timing of safety assessments and monitoring during the study.

This study will be the first administration of GSK3923868 to humans. This study aims to generate safety, tolerability and PK data of GSK3923868 in humans. A placebo control arm has been incorporated into each part of this study to allow for valid evaluation of safety and tolerability and to allow assessment of adverse events that are attributable to treatment, versus those not attributable to treatment.

Parts A (Cohorts 1 and 2) and B (Cohorts 3 and 4) will be recruiting healthy participants to allow initial assessment of the safety and tolerability of GSK3923868, before progression to treatment of participants with stable asthma in Part C (Cohort 5).

As this is a FTIH study, a sentinel dosing approach will be employed for any dose level not previously administered to humans (i.e. each increasing dose level in Part A and first repeat dosing in Part B). This will permit early assessment of the safety and tolerability of GSK3923868 in 2 participants (1 active and 1 placebo), before the remaining participants in the cohorts receive study treatment. Any escalation of doses, including definition of the next dose, will be made by the DEC based upon the review of all available safety, tolerability and plasma PK data.

Part A will employ a minimum washout period of 10 days between treatment periods to ensure sufficient time for the results of available 24 h post-dose safety data and allow for the review and any adjustment needed on the basis of emerging safety, tolerability and PK information. The washout period is based on the predicted target engagement at the planned single doses of GSK3923868, which is anticipated to be below 5% after 10 days from the time of dosing, thus it is considered sufficient washout between treatment periods.

CCI [redacted]

CCI [redacted]

In both cohorts of Part B, participants will be administered treatment for 14 days. The treatment duration will ensure a thorough assessment of safety and tolerability in the lung (target organ) and aligns with the proposed treatment duration in future patient studies.

Part C will progress once the results from Part B has been reviewed. Part C is considered necessary to inform on the early safety and tolerability profile of GSK3923868 in stable asthmatics before progression to efficacy studies where asthmatics will receive GSK3923868 on a background of HRV infection. Part C will recruit two strata of asthmatics: 1) SABA and/or intermittent ICS/LABA users who are the primary population of interest in early clinical trials, and 2) Regular ICS or ICS/LABA users to support future clinical studies and assess overall safety in treated asthma.

CCI [redacted]

4.2.1. Participant Input into Design

There was no specific elicitation of participant input into the design of this study.

4.3. Justification for Dose

For this Monodose device, the term "dose" refers to the nominal content of active pharmaceutical ingredient contained within the GSK3923868 capsules for inhalation, administered using the Monodose inhaler.

A model-based approach was utilized to provide the dose justification for this FTIH study. A Physiologically Based Pharmacokinetic (PBPK) model using GastroPlus Software was developed, in which the physico-chemical properties of the compound, *in vitro* and *in vivo* data from rats (IV and IH) and dogs (IV) PK and toxico-kinetics (TK) data were utilised [GSK Document Number 2019N419501_01]. The *in vitro* pulmonary deposition of GSK3923868 aerosolised via the Monodose inhaler was found to be CCI [redacted], when characterised using the Electronic Lung breathing simulator and subsequent *in silico* Lung Deposition Modelling using the Multiple-Path Particle Dosimetry (MPPD) model [GSK Document Number 2020N437078_01]. This value was used as input into Nasal-Pulmonary Compartmental Absorption and Transit (NPCAT) model module in GastroPlus to account for the absorption from lungs following inhalation.

The human PBPK model was determined based on the physico-chemical inputs used in the rat and dog modelling following the pre-clinical *in vivo* verification. Human intrinsic plasma clearance (37 L/h) was estimated using the rat and dog unbound clearance which

were scaled to human using restrictive liver blood flow scaling or single species allometry methods due to the absence of a robust *in vitro / in vivo* correlation. The human volume of distribution at steady state (51 L) was calculated using the mechanistic Lucokova equation used in GastroPlus [GastroPlus v9.6 User Manual, 2018].

Human PK exposure profiles in systemic circulation and lung were generated from the PBPK model, specifically for lung, the exposure was the total pulmonary compartment represented by the bronchiolar, bronchioles and alveolar interstitial. The NOAEL data obtained from the preclinical species (rats and dogs) [Section 4 of IB] was applied to derive the safety margins in both the lung and systemic compartments. In addition, the PBPK model predicted lung exposure profile was then incorporated into the PKPD model [GSK Document Number 2019N419501_01] which used the PI4KB enzyme kinetics data (accounted for competitive binding with ATP) (Section 4.2 of IB) to derive the target engagement of GSK3923868 to support dose selection.

4.3.1. Starting Dose and Dose Escalation

The proposed starting dose in Part A (SAD portion) of the study is 50 mcg. This dose was selected under the assumption that 100% of the inhaled dose would deposit into the lungs, and the predicted maximum PI4KB target engagement at this dose is < 20% (see Table 3). Based on the current knowledge on the mechanism of action of this compound, a potent inhibitor of PI4KB, a 20% target engagement is considered appropriate as minimum anticipated biological effective level (MABEL) [FDA, 2005].

In addition, the assumed 100% lung deposition following inhalation, as required by regulatory agencies, is known to be conservative. *In vitro* and *in silico* characterization of GSK3923868 aerosolised via the Monodose inhaler (GSK Document Number 2020N437078_01) suggests approximately CCI of nominal dose is likely to be deposited into the lungs. Given this predicted lung deposition, the maximum target engagement with a single 50 mcg dose is expected to be lower than 10% (see Table 3).

The planned doses for dose escalation in Part A after the first cohort with 50 mcg are 100, 250, 500, 1000, and 3000 mcg. The predicted maximum target engagement after each planned dose in Part A is outlined in see Table 3. At 3000 mcg (maximum planned dose) the predicted maximum target engagement is 97% CCI based on 100% CCI lung deposition.

Following each dose, the systemic PK (up to 24 h post dose), safety and tolerability data will be evaluated. The systemic exposure, Cmax and AUC (up to 24 h) (where data permit) will be calculated for the current dose and predicted for the next dose level assuming linear PK. The predicted Cmax and AUC will be compared with the NOAEL from IV in rats and IH in dogs. The proposed dose for the next cohort may be modified if necessary, so that the predicted Cmax and AUC are within the NOAEL from IV dose in rats.

Table 3 Predicted maximum target engagement for planned single doses of GSK3923868 at 100% CCI deposition

Planned single dose levels (µg)	Predicted Maximum Target Engagement (%)	
	100% Deposition	CCI
50	13	
100	24	
250	47	
500	69	
1000	86	
3000	97	

At these planned single doses of GSK3923868 administered via the Monodose inhaler, the predicted target engagement would be expected to be below 10% after seven days, and below 5% after 10 days from the time of dosing. This suggests that 10 days of washout between each treatment period in Part A is expected to be sufficient.

The selection of a safe dose for Part B will be performed upon consideration of available safety, tolerability and systemic PK data from Part A, and the selection of a safe dose for Part C will be performed upon consideration of available safety, tolerability and systemic PK data from Part B. The dose chosen will not exceed the maximum well tolerated dose identified in the preceding Part, and doses may be adjusted downwards if necessary.

4.3.2. Safety Margins

The planned top dose of GSK3923868 in this study is 3000 mcg. This dose was selected based on the animal to human overage in lungs, under the following assumptions: 1) 10%, 25%, 100% (as suggested by regulatory agencies) deposited dose in the lungs for rats, dogs and humans, respectively; 2) mean human body weight of 70 kg and lung weight of 1 kg; 3) NOAEL in rats and dogs following 4-week toxicology studies (Section 4 IB).

The calculation of systemic exposure safety margins is based on the model predicted systemic exposure in humans for the given doses of GSK3923868, and the toxicology studies following IV and IH in rats and IH in dogs.

Table 4 below shows the lung deposition and systemic exposure safety margins.

Table 4 Predicted GSK3923868 systemic PK parameters and safety coverage in lung and systemic following single doses of GSK3923868

Proposed daily dose to humans (µg)	Human deposited lung dose [a] (µg/g)	Predicted human AUC (ng.h/mL)	Predicted human C_{max} (ng/mL)	Ratio of animal:human deposited lung dose		Ratio of animal:human AUC			Ratio of animal:human C_{max}		
				Rat [b]	Dog [c]	Rat		Dog	Rat		Dog
						IH [d]	IV [e]	IH [f]	IH [g]	IV [h]	IH [i]
50	0.05	0.19	0.24	312	386	198	3121	889	75	2396	280
100	0.1	0.38	0.48	156	193	99	1561	445	37	1198	140
250	0.25	0.95	1.2	62	77	40	624	178	15	479	56
500	0.5	1.9	2.4	31	39	20	312	89	7	240	28
1000	1	3.8	4.8	16	19	10	156	44	4	120	14
3000	3	11.4	14.4	5	6	3	52	15	1	40	5

Key:
IH = Inhaled, IV = Intravenous.
a = assuming lung weight of 1000 g and 100% of inhaled dose is deposited in lungs.
b = actual mean body weight of 0.328 kg, actual mean lung weight of 1.305 g and assuming 10% of inhaled dose is deposited in lungs. NOAEL = 620 µg/kg/week.
c = actual mean body weight of 9.07 kg, actual mean lung weight of 96.9 g and assuming 25% of inhaled dose is deposited in lungs. NOAEL = 826 µg/kg/week.
d = gender-average AUC on Day 28 of 4-week inhalation toxicity study at NOAEL = 37.7 ng.h/mL.
e = gender-average AUC on Day 29 of 4-week intravenous toxicity study at NOAEL = 593 ng.h/mL.
f = gender-average AUC on Day 28 of 4-week inhalation toxicity study at NOAEL = 169 ng.h/mL.
g = gender-average C_{max} on Day 28 of 4-week inhalation toxicity study at NOAEL = 17.9 ng/mL.
h = gender-average C_{max} on Day 29 of 4-week intravenous toxicity study at NOAEL = 575 ng/mL.
i = gender-average C_{max} on Day 28 of 4-week inhalation toxicity study at NOAEL = 67.1 ng/mL.

4.3.3. Predicted Target Engagement at Steady State

Under the once daily dosing regimen, the steady state target engagement is predicted from the PBPK model and the PKPD model for a range of doses within the dose range proposed for this study (50-3000 mcg) as shown in Figure 1.

Simulations show that following once daily (QD) dosing, the predicted target engagement profile reaches steady state after about four days of dosing. At steady state, the peak target engagement is CCI for dose of 3000 mcg QD, while at trough (24 h post dose), there is about CCI target engagement with this dose regimen.

Although there is no established relationship of how much target engagement is required to provide potential efficacy in HRV, a murine prophylactic model of coxsackie virus-induced pancreatitis (a virus that also replicates through PI4KB) showed that clinical efficacy may potentially be achieved at a relatively lower level (above 50%) of target engagement [GSK Document Number 2019N419501_01]. It is anticipated the proposed dose range in this study will achieve 50% or greater PI4KB target engagement.

4.4. End of Study Definition

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

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

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:

5.1.1. Inclusion Criteria: Parts A and B (Healthy Participants)

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

AGE
1. Between 18 and 50 years of age inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT
2. Participants who are generally healthy as determined by medical evaluation based on screening medical history, physical examination, vital signs, ECG assessment, pulmonary function testing, laboratory tests and cardiac monitoring. • ***Note:*** *Fully resolved childhood asthma is acceptable.* • ***Note:*** *A participant with a clinical abnormality or laboratory parameter(s) not specifically listed in the exclusion or exclusion criteria that is outside the reference range for the population being studied may be included only if the investigator, in consultation with the Medical Monitor (if required), agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or outcomes.*

WEIGHT
3. Body weight at least 50.0 kg (110 lbs) and body mass index (BMI) within the range 18.5 to 32.0 kg/m^2 (inclusive).

SEX
4. Males and female participants, as follows: • **Male Participants:** A male participant is eligible to participate if they agree to the following during the intervention period and for at least 10 days after the last dose of study intervention: ○ Refrain from donating sperm. ○ Plus either: ▪ Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remaining abstinent. OR ▪ Must agree to use contraception as detailed below when having sexual intercourse with a woman of childbearing potential who is not currently pregnant: • Agree to use a male condom. • AND female partner to use an additional highly effective contraceptive method (see Appendix 4) with a failure rate of < 1 % per year. The participant should also be

advised of the benefit for a female partner as a condom may break or leak. • **Female Participants:** A female participant is eligible to participate if she is not pregnant or breastfeeding and is a woman of non-childbearing potential (WONCBP) as defined in Appendix 4.

INFORMED CONSENT
5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.1.2. Inclusion Criteria: Part C (Participants with Asthma)

AGE
1. Between 18 and 65 years of age inclusive, at the time of signing the informed consent. • ***Note:*** *Participants over the age of 50 will need to provide proof of completed COVID-19 vaccination to be eligible to participate.*

TYPE OF PARTICIPANT
2. Participants who are otherwise healthy (other than the acceptable condition of asthma and other mild atopic diseases, including allergic rhinitis and atopic dermatitis) as determined by medical evaluation based on screening medical history, physical examination, vital signs, ECG assessment, pulmonary function testing, laboratory tests and cardiac monitoring. • ***Note:*** *A participant with a clinical abnormality or laboratory parameter(s) not specifically listed in the exclusion or exclusion criteria that is outside the reference range for the population being studied may be included only if the investigator, in consultation with the Medical Monitor (if required), agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.* 3. A current confirmed physician diagnosis of asthma (as defined by the British Thoracic Society/ Scottish Intercollegiate Guidelines Network (BTS/SIGN, 2019), or the Global Initiative for Asthma (GINA, 2020 guidelines)) at least 6 months before screening. The reason for diagnosis of asthma should be documented in the participant's source data, including relevant history.

4. A screening pre-bronchodilator FEV1 ≥ 65% predicted normal value.
   Note: *Predicted values based on European Respiratory Society (ERS) guidelines [Quanjer, 2012].*
5. Participants with maintained control of their asthma using the permitted medications listed below, will be recruited as follows:

Permitted Medication Use	Number of Participants
SABA use and/or intermittent ICS/LABA use.	n=8
Regular treatment with ICS or ICS/LABA (including use of Leukotriene Receptor Agonist (LTRA))	n=8

WEIGHT

6. Body weight at least 50.0 kg (110 lbs) and body mass index (BMI) within the range 18.5 to 32.0 kg/m^2 (inclusive).

SEX

7. Males and female participants:

- **Male Participants:** A male participant is eligible to participate if they agree to the following during the intervention period and for at least 10 days after the last dose of study intervention:
  - Refrain from donating sperm.
  - Plus either:
    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remaining abstinent.

      OR

    - Must agree to use contraception as detailed below when having sexual intercourse with a woman of childbearing potential who is not currently pregnant:
      - Agree to use a male condom.
      - AND female partner to use an additional highly effective contraceptive method (see Appendix 4) with a failure rate of < 1 % per year. The participant should also be advised of the benefit for a female partner as a condom may break or leak.
- **Female Participants:** A female participant is eligible to participate if she is not pregnant or breastfeeding and is a woman of non-childbearing potential (WONCBP) as defined in Appendix 4

INFORMED CONSENT
8. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria: Parts A and B (Healthy Participants)

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. Alanine transaminase (ALT) and Aspartate Aminotransferase (AST) above upper limit of normal (ULN)[1].
3. Total Bilirubin above ULN (isolated bilirubin above ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%)[1].
4. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
5. QTcF > 450 msec at screening visit based on the average of triplicate ECGs.
6. Screening ECG measurements meets the following criteria for exclusion:

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

   - ***Note:*** *A heart rate from 100 to 110 bpm can be rechecked by ECG or vital signs within 30 minutes to verify eligibility.*
7. Medical history of cardiac arrhythmias or cardiac disease or a family or personal history of long QT syndrome.
8. Evidence of previous myocardial infarction (does not include ST segment changes associated with re-polarization).
9. Signs and symptoms suggestive of COVID-19.
   - ***Note:*** *Assessments will be performed in accordance with local site procedure.*

[1] May be repeated once before first dose.

PRIOR/CONCOMITANT THERAPY
10. Past or intended use of over-the-counter or prescription medication, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days before the first dose of study intervention, unless in the opinion of the Investigator and the GSK Medical Monitor, the medication will not interfere with the study procedures or compromise participant safety. • ***Note:*** *Use of paracetamol or acetaminophen, at doses ≤ 2 g/day and/or use of simple analgesics is acceptable.*

PRIOR/CONCOMITANT CLINICAL STUDY EXPERIENCE
11. Participation in this study would result in loss of blood or blood products in excess of 500 mL within 56 days. 12. Exposure to more than 4 new chemical entities within 12 months before the first dosing day. 13. Current enrolment or past participation in a clinical trial and has received an investigational product within the following time period before the first dosing day in this study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

DIAGNOSTIC ASSESSMENTS
14. FEV1 and FVC < 80% predicted normal value. • ***Note:*** *Predicted values based on European Respiratory Society (ERS) guidelines [Quanjer, 2012].* 15. Presence of hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention. 16. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention. • ***Note:*** *Subjects with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained* 17. 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* 18. Positive pre-study drug/alcohol screen. 19. Positive human immunodeficiency virus (HIV) antibody test. 20. Positive test for COVID-19 infection. • ***Note:*** *Testing will be according to site procedures*. 21. Current or history of drug abuse. 22. Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], Wolff-Parkinson-White (WPW) syndrome). 23. Sinus Pauses > 3 seconds. 24. Any significant arrhythmia which, in the opinion of the Investigator or GSK Medical monitor, will interfere with the safety for the individual participant. 25. Non-sustained or sustained ventricular tachycardia (with more than 3 consecutive ventricular ectopic beats).

OTHER EXCLUSIONS
26. Regular alcohol consumption within 6 months prior to the study defined as: • An average weekly intake of > 14 units for both males and females. • 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 spirits.
27. Current or previous use of tobacco- or nicotine-containing products (e.g. cigarettes, nicotine patches or electronic devices) within 6 months before screening and/or have a smoking pack history of > 5 pack years. • ***Note:*** *1 pack year = 20 cigarettes per day for 1 year or 5 cigarettes per day for 4 years.*
28. Positive breath carbon monoxide test indicative of recent smoking at screening or each in-house admission to the clinical research unit.
29. Sensitivity to any of the study interventions, or components thereof (including lactose and magnesium stearate (MgSt)), or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.
30. Participants with known COVID-19 positive contacts in the past 14 days.

5.2.2. Exclusion Criteria: Part C (Participants with Asthma)

MEDICAL CONDITIONS
1. Any asthma exacerbation requiring systemic corticosteroids within 8 weeks of screening, or that resulted in overnight hospitalization requiring additional treatment for asthma within 3 months of screening. 2. A history of life-threatening asthma, defined as an any asthma episode that required admission to a high-dependency or intensive therapy unit. 3. Significant pulmonary diseases, other than asthma, including (but not limited to): pneumonia previously requiring hospital admission, bronchiectasis, pulmonary fibrosis, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or other significant respiratory abnormalities. 4. ALT and AST above upper limit of normal (ULN)[1] 5. Bilirubin above ULN (isolated bilirubin above x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)[1]. 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. QTcF > 450 msec at screening visit based on the average of triplicate ECGs. 8. Signs and symptoms suggestive of COVID-19. • ***Note:*** *Assessments will be performed in accordance with local site procedure.*

[1] May be repeated once before first dose.

PRIOR/CONCOMITANT THERAPY
9. Past or intended use of over-the-counter or prescription medication, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days before the first dose of study intervention, unless in the opinion of the Investigator and the GSK Medical Monitor, the medication will not interfere with the study procedures or compromise participant safety. • ***Note:*** *Use of SABA, ICS and low dose ICS/LABA and LTRA is permitted for control of Asthma, and use of paracetamol or acetaminophen, at doses ≤ 2 g/day and/or simple analgesics is acceptable.*

PRIOR/CONCOMITANT CLINICAL STUDY EXPERIENCE
10. Participation in this study would result in loss of blood or blood products in excess of 500 mL within 56 days. 11. Exposure to more than 4 new chemical entities within 12 months before the first dosing day. 12. Current enrolment or past participation in a clinical trial and has received an investigational product within the following time period before the first dosing day in this study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

DIAGNOSTIC ASSESSMENTS
13. Presence of hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study intervention. 14. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention. • ***Note:*** *Subjects with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained.* 15. 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.* 16. Positive pre-study drug/alcohol screen. 17. Positive human immunodeficiency virus (HIV) antibody test. 18. Positive test for COVID-19 infection. • ***Note:*** *Testing will be according to site procedures.* 19. Current or history of drug abuse.

OTHER EXCLUSIONS
20. Regular alcohol consumption within 6 months prior to the study defined as: • An average weekly intake of > 14 units for males and females. • 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 spirits. 21. Current or previous use of tobacco- or nicotine-containing products (e.g. cigarettes, nicotine patches or electronic devices) within 6 months before screening and/or have a smoking pack history of > 5 pack years. • ***Note:*** *1 pack year = 20 cigarettes per day for 1 year or 5 cigarettes per day for 4 years.* 22. Positive breath carbon monoxide test indicative of recent smoking at screening or each in-house admission to the clinical research unit. 23. Sensitivity to any of the study interventions, or components thereof (including lactose and magnesium stearate (MgSt)), or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study. 24. Participants with known COVID-19 positive contacts in the past 14 days.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids from 7 days before the start of study intervention until discharge from the unit.

- No water is allowed until 2 hours after dosing, water is allowed ad libitum at all other times.
- Participants must fast overnight until 2 hours after each dose.

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, cola drinks, and chocolate) for 12 hours before the start of dosing until after collection of the final pharmacokinetic (PK) 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 sample.
- Participants who use tobacco or nicotine-containing products are not eligible for this study, See Section 5.2.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Unused reserve participants that meet eligibility criteria are not considered screen failures.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

ARM Name	Cohort 1	Cohort 2	Cohort 3,4	Cohort 5	Cohorts 1-5
Intervention Name	GSK3923868 Capsules for Inhalation	GSK3923868 Capsules for Inhalation	GSK3923868 Capsules for Inhalation	GSK3923868 Capsules for Inhalation	Placebo to match GSK3923868 Capsules for Inhalation
Type	Drug	Drug	Drug	Drug	Placebo
Dose Formulation	Capsule containing Inhalation powder blend Delivered via Monodose RS01 device	Capsule containing Inhalation powder blend Delivered via Monodose RS01 device	Capsule containing Inhalation powder blend Delivered via Monodose RS01 device	Capsule containing Inhalation powder blend Delivered via Monodose RS01 device	Capsule containing Inhalation powder blend Delivered via Monodose RS01 device
Unit Dose Strength(s)	50 mcg	500 mcg	500 mcg	500 mcg	N/A
Dosage Level(s)[1]	50 mcg: one capsule, single dose 100 mcg: two capsules, single dose 250 mcg: five capsules, single dose	500 mcg: one capsule, single dose 1000 mcg: two capsules, single dose 3000 mcg: six capsules, single dose	Planned dose: 3000 mcg: six capsules, daily for 14 days	Planned dose: 3000 mcg: six capsules, daily for 7 days	Number of capsules to match active treatment
Route of Administration	Inhalation	Inhalation	Inhalation	Inhalation	Inhalation
Use	Experimental	Experimental	Experimental	Experimental	Placebo
IMP and NIMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor

ARM Name	Cohort 1	Cohort 2	Cohort 3,4	Cohort 5	Cohorts 1-5
Packaging and Labelling	Study Intervention will be provided in a HDPE (high density polyethylene) bottles. Each bottle contains 21 capsules and one 8 g 20%RH maintaining desiccant sachet. Each bottle will be labelled as required per country requirement.	Study Intervention will be provided in HDPE bottles. Each bottle contains 32 capsules and one 8 g 20%RH maintaining desiccant sachet. Each bottle will be labelled as required per country requirement.	Study Intervention will be provided in HDPE bottles. Each bottle contains 32 capsules and one 8 g 20%RH maintaining desiccant sachet. Each bottle will be labelled as required per country requirement.	Study Intervention will be provided in HDPE bottles. Each bottle contains 32 capsules and one 8 g 20%RH maintaining desiccant sachet. Each bottle will be labelled as required per country requirement.	Study Placebo will be provided in HDPE bottles. Each bottle contains 32 capsules and one 8 g 20%RH maintaining desiccant sachet. Each bottle will be labelled as required per country requirement.
Current Name	N/A	N/A	N/A	N/A	N/A

[1] Any unplanned doses of GSK3923868 will be administered using combinations of 50 and 500 mcg capsules as necessary.

6.1.1. Medical Devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are the Monodose RS01 (manufacturer Plastiape S.p.A)
- Instructions for medical device use are provided in the Study Reference Manual (SRM).
- All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the Investigator throughout the clinical investigation (see Section 8.2.7) and appropriately managed by the Sponsor.

6.2. Preparation/Handling/Storage/Accountability

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.

- 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.
- Capsules should be kept in their primary packaging until dispensing into participant dosing bottles.
- Monodose RS01 devices will be supplied in bulk. After use, the devices will be placed in a plastic bag, and the bag will be labelled with the participant number, day of dosing, and date. Devices will be disposed of at site after reconciliation is verified by Study Monitor.
- 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).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- 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 Delivery Lead.
- A Safety Data Sheet (SDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.
- Precaution will be taken to avoid direct contact with the study intervention. A Safety Data Sheet (SDS) 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.

6.2.1. Dosing Procedure

Please refer to the SRM for dosing procedure.

6.2.2. Treatment Compliance

Full details of treatment compliance will be provided in the SRM.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be randomized, according to the randomization schedule generated prior to the study by the Biostatistics Department at GSK. Each participant will be dispensed blinded study intervention, labelled with his/her unique randomisation number, throughout the study. Each participant scheduled to receive study drug will receive a treatment allocation number when randomized. In Part A (Cohorts 1 and 2), Part B (Cohorts 3 and 4) and Part C (Cohort 5) participants will be randomized in a 3:1 ratio to receive study treatment (active drug: placebo).

This will be a double-blind study with participants and the site staff blinded. The site pharmacy will be unblinded. For dose escalation, the Sponsor study team physicians, statisticians, clinical safety and clinical pharmacokinetic staff and/or their delegates will have access to unblinded data, if necessary. Other Sponsor staff will remain blinded unless unblinding becomes necessary.

Once each cohort is complete, selected members of the sponsor staff may have access to unblinded PK and safety data for the given cohort, to enable the PK analysis and modelling and to support the planning of future studies.

The blind may be broken if, in the opinion of the Investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. The Sponsor study team must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, the Sponsor study team must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

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

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

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.
- A record of the quantity of GSK3923868 dispensed to and administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

As this is a first time in human study, doses may be modified on the basis of emerging safety, tolerability and PK data. The dose escalation committee (DEC) will be responsible for dose selection and/or modification. See Section 10.1.5 for more information on the committee structure.

Specific PK criteria are outlined in Section 6.5.1 and dose escalation stopping criteria are outlined in Section 6.5.2.

6.5.1. Pharmacokinetic Criteria for Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule, however in this study the maximum total daily dose will not exceed 3000 µg GSK3923868 and the maximum daily exposure of GSK3923868 is not intended to exceed the gender averaged steady-state exposure at the NOAEL in the 4-week rat intravenous toxicology study ($AUC_{(0\text{-}24h)}$ 593 ng.h/mL; C_{max} 575 ng/mL). See Section 4.3 for further details.

The following dose modification and PK stopping criteria will be used:

- If exposure in a participant is predicted to reach 593 ng.h/mL for $AUC_{(0\text{-}24h)}$ and/or 575 ng/mL for C_{max}, the dose for next cohort will be modified.
- If exposure in a participant reaches 593 ng.h/mL for $AUC_{(0\text{-}24h)}$ and/or 575 ng/mL for C_{max}, the dose escalation will be paused, and no further participants will be dosed at that level or at any higher dose level.

6.5.2. Dose Escalation Stopping Criteria

Further dosing at the current dose level stops and that dose and no higher dose may be used if any of the following occur:

- Any one participant experiences a serious adverse event that is considered at least possibly related to the study drug.
- Two participants experience a severe adverse event or bronchospasm that is considered at least possibly related to the study drug.
- Three participants meet liver chemistry stopping criteria outlined in Section 7.2.3.
- Three participants meet QTc stopping criteria outlined in Section 7.2.4.
- Three participants meet spirometry stopping criteria outlined in Section 7.2.5.
- Three participants experience any adverse event considered clinically important by the Investigator.

6.6. Treatment of Overdose

For this study, any dose of GSK3923868 greater than the planned nominal dose for the treatment period or cohort within a 24-hour time period up to minus 1 hour will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The Investigator (or physician in charge of the participant at the time) will use clinical judgement to treat any overdose.

In the event of an overdose, the Investigator (or the treating physician) should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities for 24 hours.
3. Obtain a plasma sample for PK if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

6.7. Concomitant Therapy

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

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

Participants must abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days before the first dose of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Medical Monitor, the medication will not interfere with the study procedures or compromise participant safety.

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

In Part C, depending on asthma severity participants will also be permitted to use SABA, ICS, ICS/LABA or LTRA to control their asthma.

GSK3923868 is not expected to perpetrate a drug-drug interaction (DDI) on the pharmacokinetics of these therapies; GSK3923868 is considered to pose a low risk of a systemic DDI with substrates of CYP3A4, OATP1B1 or MATE1. Montelukast is metabolised by CYP2C8. Currently there is no information on whether GSK3923868 is an inhibitor of CYP2C8, however, from the montelukast SPC coadministration of gemfibrozil (a strong CYP2C8 inhibitor) with montelukast (a sensitive CYP2C8 substrate) does not result in a clinically relevant DDI and dose adjustment is not recommended.

GSK3923868 is not expected to be a victim to a DDI with these therapies as they are not clinically relevant inhibitors/inducers of CYP450 or inhibitors of drug transporters.

6.7.1. Rescue Medicine

For asthmatics in Part C of this study SABA (e.g. salbutamol) will be permitted to be used as rescue medication. This will be provided by the participant or, if necessary, supplied by the study site.

The use of rescue medications is allowable and at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

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 be withdrawn from the study and will be asked to complete study discharge procedures as described listed in Section 7.3.

7.2. Stopping Criteria

7.2.1. Study Stopping Criteria

If one or more of the following criteria are met, the study will be temporarily paused, and all available safety data will be reviewed by the Sponsor and Investigator:

- A SAE occurring in 1 or more participants receiving GSK3923868 that is considered at least possibly related to the study drug;
- Two or more severe AEs occurring in a group of participants receiving GSK3923868 that are considered at least possibly related to the study drug.

Further participants may be dosed only if, after review, the Sponsor and Investigator considers it safe to do so.

7.2.2. Pharmacokinetic Stopping Criteria

This protocol allows some alteration from the currently outlined dosing schedule, please refer to Section 6.5.

7.2.3. Liver Chemistry Stopping Criteria

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

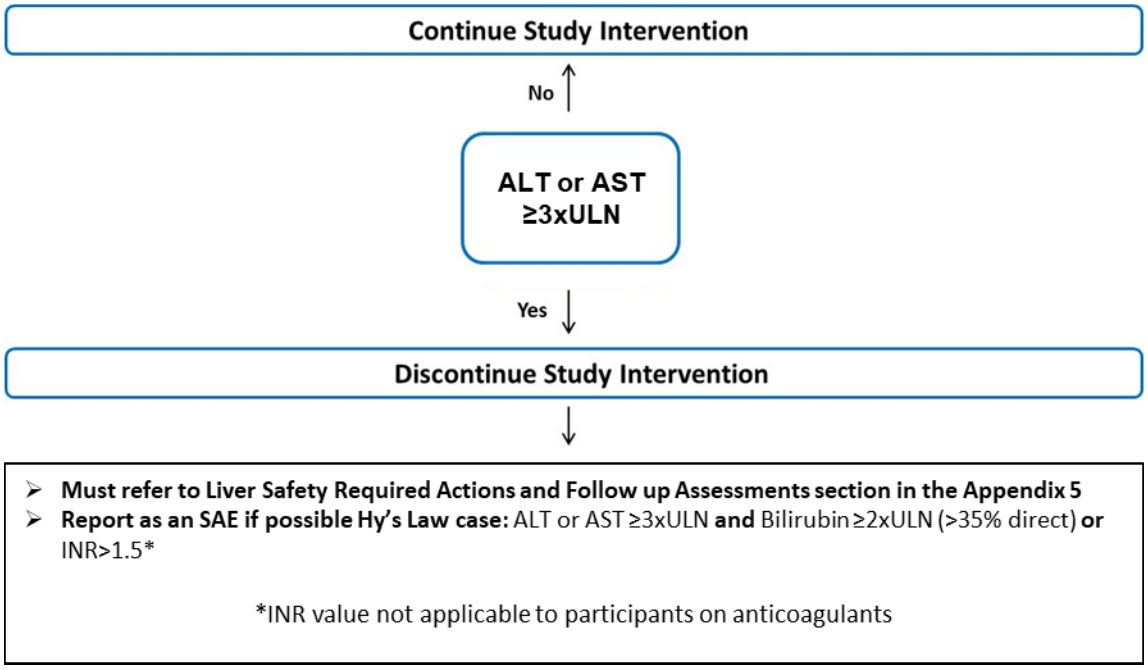
Discontinuation of study intervention for abnormal liver tests is required when:

- A participant meets one of the conditions outlined in Figure 2.

  OR

- In the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

Figure 2 Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

7.2.4. QTc Stopping Criteria

The Fridericia QT correction (QTcF) formula will be used in the study.

A participant that meets either bulleted criteria based on the average of triplicate ECG readings will be considered for withdrawal from the study intervention:

- QTcF > 500 msec
- Change from baseline: QTcF > 60 msec

Baseline QTcF will be based on the average of 3 predose ECGs collected on Day 1 (in Part A, Day 1 predose for each treatment period should be considered as baseline).

Note: Single safety ECG assessments are performed following enrolment in this study. If a single ECG should meet the criteria above, obtain two further ECGs over a brief period (e.g. 5 to 10 minutes). The averaged QTcF value of the 3 ECGs should be used to determine whether the participant should be withdrawn from the study.

7.2.5. Spirometry Stopping Criteria

Any participant experiencing a reduction in FEV1 at the 1-hour post-dose time point compared to daily predose value of > 25% in Parts A and B and > 20% in Part C will be withdrawn from the study.

7.2.6. Asthma Exacerbation Stopping Criteria (Part C Only)

Any participant experiencing an exacerbation of asthma must be withdrawn from the study. An asthma exacerbation is defined as follows:

- Episodes characterised by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function[1], i.e. they represent a change from the patient's usual status that is sufficient to require a change in treatment [GINA, 2020].
- [1]A progressive decrease in lung function is defined as sustained drop in PEF of > 20 % from baseline (Day 1, predose) maintained for ≥ 3 days. In the absence of PEF measurements, Investigator judgement will be applied.

7.2.7. Temporary Discontinuation

Participant withdrawn from the study treatment will be withdrawn from the study.

7.2.8. Rechallenge

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

7.3. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, the procedures outlined in the SOA on the day of discharge from the clinical unit should be completed (i.e. Days 2, 3, 18 and 8 for Parts A Cohort 1, A Cohort 2, B and C respectively).
- 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.
- If participants prematurely discontinue in the study, they may be replaced at the discretion of the Medical Monitor in consultation with the Principal Investigator.

In Part A, the replacement participant will be assigned to the same treatment sequence and may start the treatment period where the last participant prematurely discontinued. In Parts B and C participants will be assigned to same treatment as the participant prematurely discontinued.

7.4. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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.

7.5. Management of Participants who Develop COVID-19 Symptoms During the Study

If a participant develops COVID-19 like symptoms during the course of the study the following actions should be taken:

- During Part A (SAD portion of the study), when in the Unit participants who develop a high clinical index of suspicion for COVID-19 disease should be isolated and tested for COVID-19 in accordance with site procedures. Participants who develop symptoms suspicious of COVID-19 during washout periods should inform the site immediately.
- During Part B and C (Repeat dose of the study in HV and asthma patients), study treatment should be halted for any participants who develop a high clinical index of suspicion for COVID-19 disease; they should be isolated and tested for COVID-19 in accordance with site procedures.
- In all cases, for participants who are in the Unit, assessments should be continued as per the protocol during this period. Participants with a confirmed COVID-19 test may continue to complete safety monitoring assessments but will receive no further

doses of the study treatment. In other cases, withdrawal of participants from the study will be at the discretion of the Principal Investigator and discussed with the GSK Medical Monitor if required.

- Refer to Appendix 8 for further COVID-19 related study management details.

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.
- Individual PK data that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

  Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Additional considerations around Covid-19 can be found in Appendix 8.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.1.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, eyes, cardiovascular, respiratory, gastrointestinal and neurological systems.
- Height (at screening only) and weight will also be measured and recorded. BMI will be calculated.
- 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.
- Refer to the SRM for further information.

8.1.2. Vital Signs

- Vital signs will be measured in semi-supine position after at least 10 minutes rest and will include systolic and diastolic blood pressure, heart rate, respiratory rate and tympanic temperature.
- 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.
- Refer to the SRM for further information.

8.1.3. Electrocardiograms

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8.1.3.2. 12-Lead Safety ECGs

- Safety ECGs will be performed in semi-supine position after at least 10 minutes rest.
- All safety ECGs must be obtained using an ECG machine that automatically calculates the heart rate and measures, PR, QRS, QT and QTcF intervals.
- Safety ECGs will be printed and interpreted on-site by the Investigator to ensure participant safety. Safety ECGs may also be printed from the Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12 lead digital recorder used for continuous cardiac monitoring (see Section 8.1.3.4). At time points where triplicate ECGs are required, the ECGs will be obtained at least 2 minutes apart and over a recording period of up to 10 minutes.
- Baseline QTcF will be based on the average of 3 predose ECGs collected on Day 1 (in Part A, Day 1 predose for each treatment period should be considered as baseline).
- Refer to Section 7.2.4 for QTc specific stopping criteria.
- Refer to the SRM for further information.

8.1.3.3. Telemetry Monitoring

- In addition to 12-lead safety ECGs, participants will be monitored on telemetry for each treatment period in Part A and for the first dose in Parts B and C.

8.1.4. Lung Function

- Peak Expiratory Flow (PEF) (Part C only) and spirometry assessments will be performed as outlined in the SRM.

8.1.5. Clinical Safety Laboratory Assessments

- See 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 significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

- In Part C, abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the Investigator or Medical Monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the aetiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the SRM and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results may be recorded in the eCRF.

8.1.6. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- If a pregnancy is reported then the Investigator should inform GSK within 2 weeks of learning of pregnancy and should follow the procedures outlined in Section 8.2.5.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or as required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

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

The definitions of AE or SAEs can be found in Section 10.3.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Section 10.6. Device deficiencies are covered in Section 10.6.

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

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the start of screening until the follow-up visit at the time points specified in the SoA (Section 1.3).
- 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 as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance 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 information on 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.

8.2.2. Method of Detecting AEs and SAEs

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.

8.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3.

8.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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.
- An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

- 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

8.2.5. Pregnancy

- This study will recruit only female participants meeting the criteria of a woman of non-childbearing potential, so pregnancies are not expected. However, if a pregnancy does occur then procedure outlined here should be followed.
- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 10 days after the final dose.
- 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 the foetal status (presence or absence of anomalies) or indication for procedure.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.2.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.2.6. Cardiovascular and Death Events

The requirements outlined in this section do not apply to healthy participants in Parts A and B.

For Part C, any cardiovascular (CV) events detailed in Appendix 3 Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular and Death

sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

8.2.7. Medical Device Deficiencies

Medical devices are being provided for use in this study. To fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 10.6.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

8.2.7.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.
- The method of documenting Medical Device Incidents is provided in Section 10.6.

8.2.7.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.2.7.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a device deficiency.

- The Medical Device Deficiency Report Form will be sent to the sponsor by facsimile transmission. If facsimile transmission is unavailable, then notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.2.7.4. Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.3. Pharmacokinetics

8.3.1. Plasma Sample Collection

Plasma samples will be collected for measurement of plasma concentrations of GSK3923868 as specified in the SoA (Section 1.3). Details of sample collection will be provided in the SRM.

- A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of plasma PK samples 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 or longer than 24-hour post dose) to ensure appropriate monitoring and characterisation of GSK3923868 plasma PK profile.
- 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.
- Samples collected for analyses of GSK3923868 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 plasma samples. Participant confidentiality will be maintained. Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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8.4. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.5. Biomarkers

Biomarkers are not evaluated in this study.

8.6. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.7. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

Reporting of study data will be performed in accordance with applicable GSK and/or contract research organization (CRO) standards. Complete details of the planned statistical analyses will be provided in the Statistical and Analysis Plan (SAP).

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

9.1. Statistical Hypotheses

Given this study is the FTIH for GSK3923868, no formal statistical hypotheses will be tested. The primary objective is to evaluate the safety and tolerability of GSK3923868 in healthy participants and stable asthmatics.

9.2. Sample Size Determination

No formal statistical techniques were used to calculate the sample size for this study.

The number of participants included is deemed an adequate number to provide an assessment of safety and tolerability and pharmacokinetics measurements, and thereby to allow progression to larger clinical studies.

A minimum of 5 participants receiving each dose of active drug (either as a single or repeat dose) are required for the dose escalation meetings. With 5 participants, if the true adverse outcome rate is 5%, the chance of not observing any adverse events at a given dose is 77%. If the true adverse outcome rate is 20%, the chance of not observing any adverse events at a given dose level is 33%.

For Part A, sufficient healthy adult participants will be screened to ensure a total of 12 participants per cohort are randomised with the aim to achieve approximately 12 per cohort completed.

In total for Part A, 9 participants are planned to receive each dose of active drug in each period. If the true adverse outcome rate is 5%, the chance of not observing any adverse events at a given dose is 63%. If the true adverse outcome rate is 20%, the chance of not observing any adverse events at a given dose level is 13%.

In Part B, sufficient healthy adult participants will be screened to ensure 8 participants are randomised to each of the two cohorts, with the aim to achieve approximately 8 completed in each cohort.

For Part C, sufficient participants with asthma will be screened to ensure 16 participants are randomised, with the aim to achieve 16 completers. Part C will be randomised according to two strata, SABA and/or intermittent inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination users and ICS or ICS/LABA users.

In Parts B and C, 12 participants are planned to receive each dose of active drug. The corresponding probabilities for 12 participants with true event rates of 5% and 20% are 54% and 7%, respectively.

This level of predictivity is deemed adequate within this phase of development.

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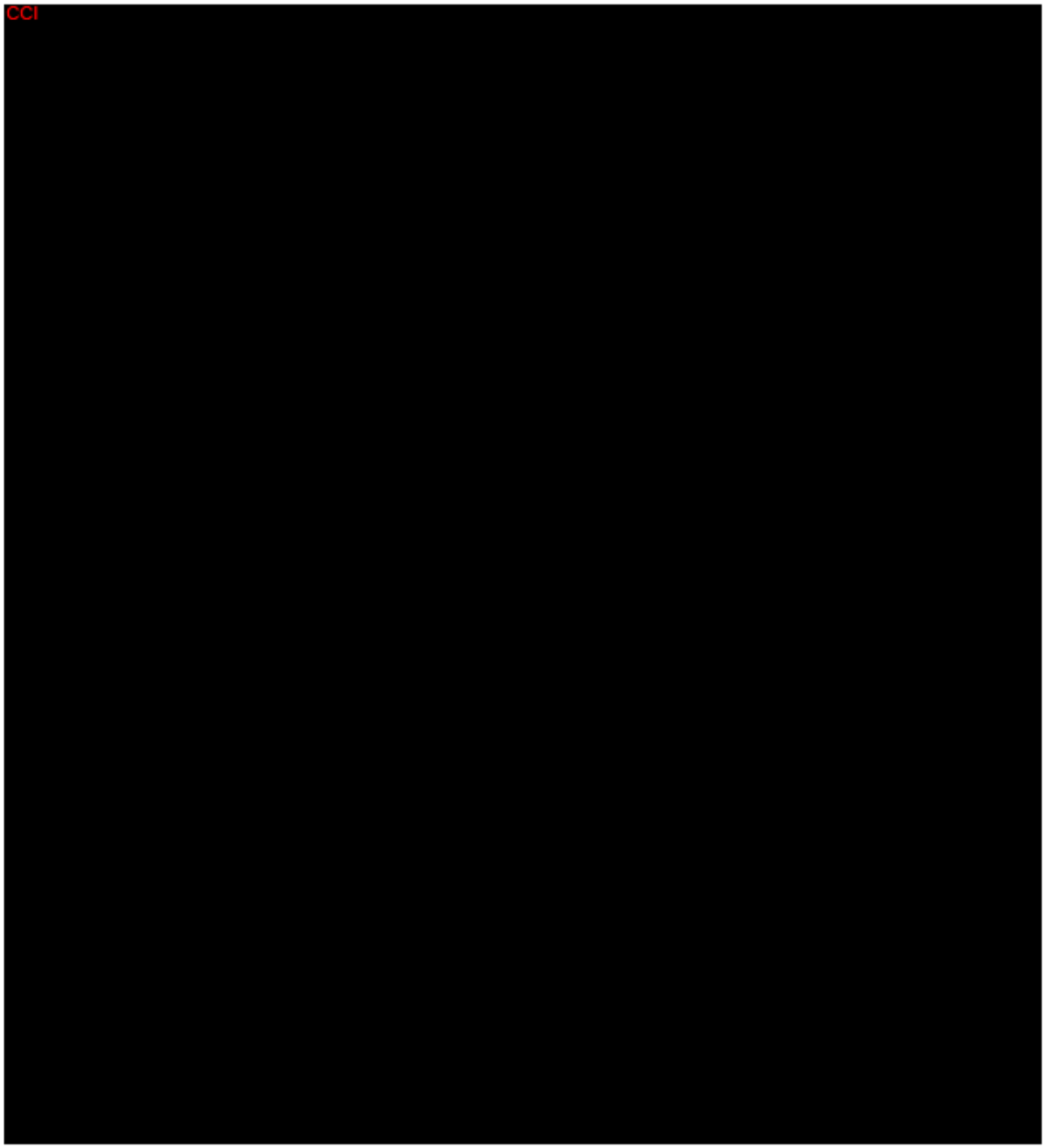

For Parts A, B and C if participants prematurely discontinue in the study, they will be replaced at the discretion of the sponsor Medical Monitor in consultation with the Principal Investigator.

9.3. Analysis Sets

Participant Analysis Set	Description
Screened	All participants who were screened for eligibility.
Enrolled	The All Subjects Enrolled (ASE) population will consist of all participants who enrolled in the study. Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled analysis set as they did not enter the study.
Randomized	The randomized population will consist of all participants who were randomized. A participant who is recorded as a screen failure and was also randomized will be considered as randomized in error provided that they have not performed any study assessments.
Safety	All randomized participants who received at least 1 dose of study intervention. Participants will be analysed according to the treatment they received.
Pharmacokinetic (PK)	All randomized participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). Participants will be analysed according to the treatment they received.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database release and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary Endpoint(s)

All safety analyses will be performed on the Safety Population and details will be provided in the SAP.

9.4.1.1. Adverse Events and Serious Adverse Events

The proportion of participants reporting AEs will be tabulated by study intervention and by cohort and dose for participants on GSK3923868, except for Part B for which data from cohorts 3 and 4 will be combined (the cohorts are identical in every aspect apart from the timing of the bronchoscopy assessment). AEs will also be tabulated by severity and relationship to study product. AEs will be tabulated using MedDRA preferred terms.

The number and percentage of participants experiencing each specific AEs (All AEs, Grade 2 or higher, and SAEs) will be tabulated by severity and by relationship to study product. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity or the strongest relationship to study product.

AEs leading to withdrawal will also be summarized by study intervention.

9.4.1.2. Laboratory values, vital signs, 12-lead electrocardiogram and Spirometry

Whilst all data collected will be summarized, only measurements which are clinically significant at any timepoint between randomisation and follow up will be reported as part of the primary endpoint. Potential clinical interest (PCI) ranges will be defined in the SAP.

This data includes:

- Laboratory results for haematology, clinical chemistry and urinalysis (see Appendix 2 for full details).
- Vital Signs measurements for semi supine systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature
- 12-lead safety electrocardiogram (ECG) measurements for heart rate, PR, QRS, QT and QT interval corrected for heart rate according to Frederica's formula (QTcF) intervals
- Spirometry measurements for FEV_1 and FVC

9.4.2. Secondary Endpoint(s)

All pharmacokinetic analyses will be performed on the Pharmacokinetic Population.

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modelling and Simulation (CPMS) department within GlaxoSmithKline.

Plasma GSK3923868 concentration-time data will be analysed by non-compartmental methods with WinNonlin. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined if data permitting, for each dose of GSK3923868:

- Part A, Cohorts 1 & 2: AUC(0-t), AUC(0-∞), Cmax and Tmax
- Part B, Cohorts 3 & 4: Cmax, Tmax and AUC(0-τ) on Day 1 and Day 14 (τ=24h for once a day dosing regimen)
- Part C, Cohort 5: Cmax, Tmax and AUC(0-τ) on Day 1 and Day 7 (τ=24h for once a day dosing regimen.

If AUC(0-τ) is not calculatable due to non-quantifiable plasma GSK3923868 data, AUC(0-t') may be calculated instead. t' is the common timepoint for all subjects for the corresponding dose or cohort.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarised descriptively. Analysis of dose proportionality (Part A) and dose accumulation (Parts B and C) will be conducted. A population PK model (POP PK) may be developed with all available data as appropriate and may be reported separately. Further details of the analysis plan and methods will be defined within the SAP.

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9.5. Interim Analysis

There are no formal interim analyses conducted as part of this study, however the following in-stream analyses will be performed.

9.5.1. Dose Escalation Committee (DEC)

A review of preliminary safety, tolerability and plasma PK data will be conducted by the DEC prior to each dose level in Part A, before initiating repeat dosing in Part B, and before repeat dosing asthmatics in Part C.

Safety and tolerability data will be provided by the site at the end of each dosing session, along with analysis of the plasma PK data which will be performed using nominal sampling times.

To minimize the risk of unblinding during DEC meetings, individual PK data will be scrambled such that the blind is maintained. Summary statistics will also be provided for plasma PK parameters (Cmax and AUC). The data may be unblinded should a safety concern arise during the blinded review.

Additional details are available in the Dose Escalation Plan.

9.5.2. Instream Analysis of PK Data

Once Cohort 3 has completed, selected members of the GSK sponsor staff team will be formally unblinded to the treatment allocations of participants who completed the study to

enable the analysis and modelling of PK data to start. Once Cohort 4 has completed, the same sponsor staff will also be unblinded to the treatment allocations of the completed participants from Cohort 4 to incorporate their data into the ongoing PK analysis and modelling. Access to unblinded subject-level data will be restricted to members of the Statistics and Programming and Clinical Pharmacology Modelling and Simulation teams. The aim of this analysis is to inform internal decision making around dose selection for future studies in the development plan of this compound. This analysis will not impact the conduct or the design of the current study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- 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.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days of their first dose.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3923868 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have GSK3923868 approved for medical use or approved for payment coverage.

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 who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Dose Escalation Committee

As this study represents the first administration of GSK3923868 to humans, a dose escalation committee (DEC) will be responsible for reviewing all available safety, tolerability and PK data to determine progressing dose levels in Part A and before initiating repeat dosing in Parts B and C.

The DEC will at a minimum consist of the following:

- Principal Investigator (or suitably qualified delegate)
- From GSK:
    - Medical Monitor
    - Clinical Pharmacology, Modelling and Simulation representative
    - Safety and Medical Governance representative
    - Statistician

To minimise the risk of unblinding during DEC meetings, individual PK data will be scrambled such that the blind is maintained. Summary statistics will also be provided for plasma PK parameters (Cmax and AUC). The data may be unblinded should a safety concern arise during the blinded review. Dose modification and escalation stopping criteria are outlined in Section 6.5. Further details on the dose escalation process and DEC are outlined in the Dose Escalation Plan.

10.1.6. 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 all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-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. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this 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.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on 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.
- Guidance on completion of CRFs will be provided in the **eCRF Completion Guidelines Document** Veeva Vault Location.
- Quality tolerance limits (QTLs) will be pre-defined in the Veeva Vault system to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Specific Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR) / equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records

may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Document Agreement (SDA) template as per SOP52563: provided by CRA to outline what will be regarded as source data per study. SDA is finalised by CWM (on behalf of the PI) and CRA (on behalf of the sponsor) and stored in the SIF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

10.1.10. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the local and central labs.
- 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.

Table 5 Protocol Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Urea	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose non-fasting	Calcium[2]	Alkaline phosphatase	
Coagulation	Prothrombin time (PT)	Activated partial thromboplastin time (aPTT)		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood, protein or leukocyte is abnormal)			
Pregnancy testing	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test.			

Laboratory Assessments	Parameters
Other Screening Tests[3]	• Follicle-stimulating hormone and oestradiol (as needed in women of non-childbearing potential only). • Alcohol Breath Test • Breath Carbon Monoxide Test • Urine drug screen[4] (to include at minimum: amphetamines, methamphetamine, barbiturates, cocaine, opiates, cannabinoids, benzodiazepines, methadone, phencyclidine and tricyclic antidepressants). • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody). • COVID-19 testing will be in line with local site procedure.

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 7.2.3 and Section 10.5 All events of ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. Corrected Calcium
3. The investigative site may assess other laboratory parameters as needed, according to standard site practice and results will be recorded in source documents.
4. The investigative site may screen for additional drugs of abuse as part of standard site practice and will be recorded in source documents. The study eCRF will only collect drug screen results of those that are positive

.

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

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New 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 intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether

"hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT or AST≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: 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 considering 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 submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. 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) 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 the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Definitions:

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

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

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

2. Postmenopausal female

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

   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

All male participants must agree to using a male condom when having sexual intercourse with a female partner of childbearing potential who is not currently pregnant as outlined in Section 5.1.

Female partners of childbearing potential who are not currently pregnant must use an additional highly effective contraceptive method with a failure rate of < 1 % per year, as outlined in the table below:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent

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

• Progestogen-only hormone contraception associated with inhibition of ovulationc
  • oral
  • injectable

• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*

a. Contraceptive use 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 amenorrhea method (LAM) are not acceptable methods of contraception for this study.

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT or AST - absolute</td><td>ALT or AST ≥3xULN
If ALT or AST ≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or <u>international normalized ratio (INR)</u> >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 participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT or AST ≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 24 h of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form</td></tr>
</table>

Liver Chemistry Stopping Criteria	
If ALT or AST ≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT or AST ≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week) [James, 2009]. **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 or AST ≥ 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 or AST ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT or AST ≥ 3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

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10.6. Appendix 6: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.6.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event **that:**
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. 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. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

• Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.6.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.6.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • 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/device deficiency form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant 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. • For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency. o A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a

device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one 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 used for rating the intensity of an event; both AEs and SAEs 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.
- Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- 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, in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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 assess causality for every event before the initial transmission of the SAE data to GSK.

- The investigator may change his/her opinion of causality considering 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/SAE/device deficiency

- 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/SAE/device deficiency 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, if conducted.
- 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.

10.6.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an 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 table) 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.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE 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 GSK medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in study reference manual (SRM).

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the GSK medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper 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 paper data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM.

10.6.6. Reporting of SADEs

SADE Reporting to GSK
• NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found in SRM.

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10.8. Appendix 8: Covid-19

10.8.1. Overall Rationale for this Appendix

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

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

These measures will remain in place until study completion.

10.8.2. Study Procedures During COVID-19 Pandemic

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

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

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

10.8.3. Protocol Defined Procedures/Visits:

- The protocol defined interval for the collection of samples during the Follow-up visit (see Section 1.3 Schedule of Activities), may be extended up to a maximum length of 14 days.

10.8.4. Data Management/Monitoring:

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

Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.9. Appendix 9: Abbreviations and Definitions and Trademarks

ADE	Adverse devise effect
AE	adverse event
ALT	alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASE	All subjects enrolled
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUC(0-∞)	area under the concentration-time curve from time 0 (predose) extrapolated to infinite time
AUC(0-24)	area under the concentration-time curve from time 0 (predose) to 24 hours post dose administration following the first dose
AUC(0-t)	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC(0-τ)	area under the concentration-time curve from time 0 (predose) to time tau
AV	atrioventricular
CCI [redacted]	
BMI	body mass index
bpm	beats per minute
BTS	British Thoracic Society
CA	Competent Authorities
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence interval
Cmax	maximum observed concentration
COVID	Coronavirus disease
COPD	Chronic obstructive pulmonary disease
CPEM	Clinical Pharmacology and Experimental Medicine
CPK	creatine phosphokinase
CPMS	Clinical Pharmacokinetics Modelling and Simulation
CRA	Clinical research
CRO	Contract research organization
CRF	Case report form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
CWM	Clinical ward manager
CYP	cytochrome P450
DDI	drug-drug interaction
DEC	Dose escalation committee
DMPK	Drug metabolism and Pharmacokinetics
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form

CCI	
ERS	European Respiratory Society
FEV1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FTIH	First time in human
FVC	forced vital capacity
g	Gram
GCP	Good Clinical Practice
GCSP	Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HR	Heart rate
HRT	hormone replacement therapy
HRV	Human rhinovirus
IB	Investigator's Brochure
lbs	pounds
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
IH	Inhaled
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
kg	kilogram
LDH	lactate dehydrogenase
LABA	long-acting beta agonist
LAM	lactational amenorrhea method
LTRA	Leukotriene Receptor Agonist
m^2	square meter
MABEL	minimum anticipated biological effective level
MATE	multidrug and toxin extrusion
mcg	microgram
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDR	Medical Device Regulation
mg	milligram
MgSt	magnesium stearate

mL	milliliter
mm	millimeter
msec	millisecond
mV	Megavolt
n	number
NIMP	Non Investigational Medicinal Product
NOAEL	No Observed Adverse Effect Level
NQ	Non-quantifiable
PBPK	Physiologically-based pharmacokinetics
PCI	Potential clinical interest
PEF	Peak Expiratory Flow
PI	Principle investigator
PK	pharmacokinetic(s)
PKPD	pharmacokinetic/pharmacodynamic modelling
PT	Prothrombin time
QD	once a day
QTc	corrected QT interval; the measure of time between the start of the Q wave and the end of the T wave
QTcF	corrected QT interval using the Fridericia formula
QTL	quality tolerance limit
RBC	Red blood cell count
RNA	ribonucleic acid
RH	Relative humidity
SABA	short-acting beta agonist
SAE	serious adverse event
SADE	serious adverse device event
SAP	Statistical and Analysis Plan
SD	Standard deviation
SDA	Source Document Agreement
SGOT	Serum Glutamic-Pyruvic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SIGN	Scottish Intercollegiate Guidelines Network
SoA	schedule of activities
SD	single dose
SDS	Safety Data Sheet
SOP	Standard operating procedures
SPC	Summary of product characteristics
SRM	Study reference manual
SUSAR	suspected unexpected serious adverse reactions
t1/2	terminal phase half-life
Tmax	time to reach maximum observed plasma concentration
QC	Quality check
ULN	upper limit of normal
USADE	Unanticipated serious adverse device event
Vz/F	apparent volume of distribution
WBC	White blood cell count

WONCPB	Wome(a)n of nonchildbearing potential
WPW	Wolff-Parkinson-White

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
GastroPlus
MedDRA
RS01 Monodose dry powder inhaler
WinNonlin

10.10. Appendix 10: Protocol Amendment History

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE.

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 04	*24 Sep 2021*	TMF-13791516
Amendment 03	*15-FEB-2021*	2020N430088_03
Amendment 02	*07-SEP-2020*	2020N430088_02
Amendment 01	*28-AUG-2020*	2020N430088_01
Original Protocol	*17-Jul-2020*	2020N430088_00

Amendment [03]: 15-FEB-2021

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

Overall Rationale for the Amendment

This amendment has been prepared to:

- Extend the PK sampling period from 24 hours to 48 hours in Part A Cohort 2 to enable a better estimation of the drug terminal half-life and prediction of repeat dose PK profile. The participants in this cohort will also be discharged on Day 3 (48 hours post dose).
- Update the dose modification criteria and maximum daily exposure limits to align with the NOAEL in the 4-week rat intravenous study. To date, the 50 and 100 mcg treatment periods in Part A (SAD) have been completed with no notable safety or tolerability findings.
- Allow the unblinding of data following the completion of each cohort in Part B to enable analysis and modelling of PK data to start.

Specific details of the changes are provided below:

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis	Changes to treatment period dates and discharge time	To enable discharge information to be captured
Section 1.3 Schedule of Activities	Part A: Single Ascending Dose Healthy Participants (Cohort 2). Addition of 48h Blood	Split of cohort 1 and cohort 2 activities into separate tables to accommodate the addition of PK sample to enable calculation of

Section # and Name	Description of Change	Brief Rationale
	PK sample and discharge activities moved to Day 3	terminal half-life and enable discharge information to be captured
Section 4.1 Overall design -	Table 1. Changes to treatment period dates and discharge time	To enable discharge information to be captured
Section 4.3.1 Starting Dose and Dose Escalation	Updated text for the IV dose in rats	Dose modification criteria updated to align with NOAEL
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Updated text to define timing of unblinding Added text to clarify access to unblinded data	To enable modelling of PK data to start after cohort 3 To clarify which lines would have access to unblinded subject-level data after cohort 3 is complete
Section 6.5.1 Pharmacokinetic Criteria for Dose Modification	Rat IV data used to calculate PK dose exposure	Dose modification criteria updated to align with NOAEL
Section 7.3 Participant Discontinuation/Withdrawal from the Study	Day of discharge extended to day 3	Updated discharge information
Section 9.4.1.1 Adverse Events and Serious Adverse Events	Cohort 3 and 4 data will be pooled and reported together Addition of text to include the cohorts being reported	As cohorts 3 and 4 are identical in every aspect expect the timing of bronchoscopy assessment, data from the two cohorts will be pooled and reported together
Section 9.5.2 Instream Analysis of PK Data	Updated text to define timing of unblinding Added text to clarify access to unblinded data	To enable modelling of PK data to start after cohort 3 To clarify which lines would have access to unblinded subject-level data after cohort 3 is complete

Amendment [02]: 07-SEP-2020

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

Overall Rationale for the Amendment

This amendment is in response to questions raised by the Research Ethics Committee in the UK. The committee requested clarification on the withdrawal criteria for subjects who become COVID-19 positive, during the study.

Section # and Name	Description of Change	Brief Rationale
Section 7.5 Management of Participants who Develop COVID-19 Symptoms During the Study	Clarification on the management of the participants who become COVID-19 positive, during the study	Clarification that participants that test positive for COVID-19 will receive no further doses of study treatment but continue with safety monitoring whilst in the unit

Amendment [01]: 28-AUG-2020

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

Overall Rationale for the Amendment

This is amendment is in response to questions raised in the MHRA's Grounds for non-acceptance letter which was received on the 20 August 2020 and includes justification for planned doses, addition of dose escalation stopping criteria, clarification to study stopping criteria, liver chemistry criteria, clarifications to contraceptive requirements and minor updates to references.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Addition of text around the dose modification and stopping criteria.	To clarify the dose escalation process.
Section 4.1 Overall Design	Addition of text around the dose modification and stopping criteria.	To cross reference the dose escalation stopping criteria and dose escalation committee (DEC) structure.
Section 4.3.1. Starting Dose and dose escalation and Table 3	Addition of text and table on predicted target engagement for planned dose levels.	To add further information on the predicted maximum target engagement for Part A dose levels.
Section 4.3.2 Safety Margins	Update to the table numbering in the protocol.	Correction to table numbering as a new table was inserted into Section 4.3.1.
Section 4.3.3. Predicted Target Engagement at Steady State	Addition of text and figure on predicted target engagement.	To add further information on the predicted target engagement profiles for different repeat dose levels.
Section 5.1.1 Inclusion criteria: Parts A & B (Healthy participants) No.4	Contraception changes to male contraception usage when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.	Clarification to contraception requirements for male participants and their female partner of childbearing potential.
Section 5.1.2 Inclusion criteria: Parts C (Participants with Asthma) No.8	Contraception changes to male contraception usage when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.	Clarification to contraception requirements for male participants and female partner of childbearing potential.

Section # and Name	Description of Change	Brief Rationale
Section 6.5 Dose Modification	Addition of references to dose modification and stopping criteria.	To cross reference the dose escalation stopping criteria and DEC committee structure.
Section 6 .5.1 Pharmacokinetic Criteria for Dose Modification	Update to Pharmacokinetic (PK) Criteria for Dose Modification.	To clarify that if PK exposure limit is reached, there will be no further dosing of participants at that dose or any higher dose level.
Section 6.5.2 Dose Escalation Stopping Criteria	Addition of dose escalation Stopping Criteria.	To outline specific criteria for stopping dose escalation.
Section 7.2.1 Study Stopping Criteria	Clarification for study stopping criteria.	To clarify that dosing will be paused should two or more severe adverse events (AEs) related to the study drug occur.
Section 7.2.3 Liver Chemistry Stopping Criteria & Figure 1	Addition of aspartate aminotransferase (AST) level to liver chemistry stopping criteria.	Update to include AST in the figure.
Section 10.1.5.1 Dose Escalation Committee	Clarification in Dose escalation committee.	Cross reference update to the dose modification and escalation stopping criteria.
Section 10.2 Appendix 2: Clinical Laboratory Tests & Table 5	Addition of AST to liver chemistry stopping criteria and update to table numbering.	Footnotes updated to correctly cross reference liver chemistry stopping criteria & addition of AST to liver chemistry stopping criteria.
Section 10.3.2 Definition of SAE	Addition of AST to liver chemistry stopping criteria.	Addition of AST to liver chemistry criteria.
Section 10.4.2 Appendix: 4 Contraceptive Guidance	Edit to the Appendix 4 title.	Update to title to remove barrier.
Section 10.4.2 Contraception Guidance	Update to the male contraception guidance.	Added male contraception and female partner's guidance.

Section # and Name	Description of Change	Brief Rationale
Section 10.5 Appendix 5 Liver Safety: Required Actions and Follow up Assessments	Addition of AST to liver chemistry stopping criteria added to table.	Addition of AST to Liver Chemistry stopping criteria.
Section 10.7 Appendix 7	Update to the table numbering in the protocol.	Correction to table numbering as a new table was inserted into Section 10.7

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