TITLE PAGE

Protocol Title: A single-centre, double-blind (sponsor open), placebo controlled two part study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK2292767 as a dry powder in healthy participants who smoke cigarettes.

Protocol Number: 202062

Short Title: Double-blind (sponsor open), placebo controlled study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK2292767 in healthy participants who smoke cigarettes.

Compound Number: GSK2292767

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information will be provided separately.

Regulatory Agency Identifying Number(s): 2016-003188-21

Approval Date: 05-JAN-2017

SPONSOR SIGNATORY:

PPD

5th January 2017

Tony Cahn
Head Respiratory TAU

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	05-JAN-2017
Original Protocol	14-OCT-2016

Amendment 1 05-JAN-2017

Overall Rationale for the Amendment: This protocol amendment was created to incorporate the comments received from the Regulatory Authorities in the UK (MHRA).

Section # and Name	Description of Change	Brief Rationale
9.1.1 Time Period and Frequency for Collecting AE and SAE Information	*Previous Text*: All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. *Revised Text:* All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.	To comply with regulation - UK Statutory Instrument 2004 No 1031 Part 5 and EC Guidance document 2011/C 172/01 (CT-3)
8.1.4 Safety Stopping Criteria	*Previous Text:* None *Revised Text:* Dose escalation stopping criteria include the following: • A serious adverse event (SAE) occurring in 1 or more participants receiving GSK2292767 that is considered at least possibly related to study drug; • Two or more severe adverse events occurring in a group of participants receiving GSK2292767 that are considered at least possibly related to study drug.	To ensure participant safety for Part A - single dose escalation.
6.1. Inclusion Criteria	*Previous Text:* A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during	To provide guidance on the duration of male contraception use and exclusion of sperm donation.

Section # and Name	Description of Change	Brief Rationale
Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information	the treatment period and for at least from the time of first dose of study medication until at least five half-lives of study medication after the last dose of study medication and refrain from donating sperm during this period. *Revised Text:* A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least from the time of first dose of study medication until at least 55 (5x11) hours plus an additional 90 days after the last dose of study medication and refrain from donating sperm during this period. GSK2292767 has a predicted half-life of approximately 11 hours. *Previous Text:* Refrain from donating sperm for duration of study and for 5 half-lives + 90 days after the last dose of drug. *Revised Text:* Refrain from donating sperm for duration of study and for at least 55 hours plus an additional 90 days after the last dose of drug.	
Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information	*Previous Text:* Table 7, Note B - Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 5 half-lives + 90 days after	Only WONCB permitted in study, text removed for clarity.

Section # and Name	Description of Change	Brief Rationale
	the last dose of study treatment *Revised Text:* Note B, removed	
2.2 SOA – Part A (Single Dose)	*Previous Text:* None *Revised Text:* Predose PK Urine sample added to Part A Schedule of Activities	Predose PK urine sample required for complete analysis
7.4 Blinding	*Previous Text:* Blinded study with unblinded site pharmacist who is dispensing drug. In order to maintain this blind, an unblinded site pharmacist will be responsible for the dispensation of all study treatment. This unblinded site pharmacist will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study treatment with the investigator. *Revised Text:* Blinded study with unblinded site pharmacy staff who are labelling and ensuring release of the study drug In order to maintain this blind, unblinded site pharmacy staff will be responsible for labelling and ensuring release of the blinded study treatment to the investigator or designee.	Process for dispensing drug updated to reflect site procedures.

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1. SYNOPSIS

Protocol Title: A single-centre, double-blind (sponsor open), placebo controlled two part study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK2292767 as a dry powder in healthy participants who smoke cigarettes.

Short Title: Double-blind (sponsor open), placebo controlled study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK2292767 in healthy participants who smoke cigarettes.

Rationale: This study is the first administration of GSK2292767 to humans. The study will evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single and repeat inhaled doses of GSK2292767 in healthy smokers. This study is intended to provide sufficient confidence in the safety of the molecule and preliminary information on target engagement to allow progression to further repeat dose and proof of mechanism studies.

Objectives and Endpoints:

Objective	Endpoint
Primary	

• To assess the safety and tolerability of single and repeat doses of GSK2292767 as a dry powder in healthy cigarette smokers.	• Safety and tolerability of GSK2292767 as assessed by clinical monitoring of:
	  • Vital Signs
	  • Spirometry
	  • Electrocardiogram (ECG)
	  • Laboratory safety data
	  • Adverse events (AEs)

Secondary	
• To determine the pharmacokinetic profile of single and repeat doses of GSK2292767 as a dry powder in healthy cigarette smokers.	• GSK2292767 plasma concentration data and derived pharmacokinetic parameters including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}),terminal half-life ($T_{1/2}$) and trough concentrations ($C\tau$) following single and repeated dry powder doses, where data allow.
• To investigate the steady-state trough concentration of GSK2292767 in lung epithelial lining fluid (ELF) and Bronchoalveolar lavage (BAL) cell pellet after repeat inhaled dry powder	• BAL concentrations of GSK2292767 and derived lung ELF and cell pellet deposition parameters.

Objective	Endpoint
administration in healthy cigarette smokers.	
Exploratory	
• To determine the pharmacodynamic effect of GSK2292767 on the biomarker Phosphatidylinositol (3,4,5)-trisphosphate (PIP3) in induced sputum after single and repeat doses of GSK2292767administered as a dry powder in healthy cigarette smokers.	• PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area) in induced sputum cells.
• To explore the intracellular distribution, binding and lysosomal disposition of GSK2292767 from lung resident cells derived from bronchoalveolar lavage at steady-state following repeat administration	• Semi quantitative characterisation of intracellular distribution of GSK2292767 within lung resident cells, binding and lysosomal uptake and retention.
• To generate samples that will be used to characterise the metabolic profile of GSK2292767 in plasma, following single and repeat doses of GSK2292767 administered as a dry powder in healthy cigarette smokers.	• Characterisation and quantification of metabolites in plasma.
• To collect urine samples only at the highest proposed dose level to characterise the renal excretion of systemically available drug following inhaled delivery.	• Semi-quantitative characterisation of amount of parent GSK2292767 excreted in urine

Overall Design: This is a two part, single site, randomised, double-blind (sponsor open), placebo controlled study in healthy smokers.

Part A will consist of two 3-period interlocking cohorts to evaluate the safety, tolerability and pharmacokinetics of ascending single doses of GSK2292767 administered as a dry powder. Pharmacodynamic effects on biomarkers will also be assessed.

- In each cohort 16 participants will be randomised to one of four treatment sequences. 12 participants will receive placebo in one of the periods, where as four participants will receive the active dose in all periods.
- The planned doses of GSK2292767 for this study are 50, 100, 200, 500, 1000 and 2000 μg.
- On the first day of dosing within each period, only two participants will be dosed (randomisation schedule designed so that one placebo and one active will be dosed on first day). Following review of the safety data for the first set of

participants, and assuming no safety concerns, the remaining participants will be dosed.
- Following each dose level, safety data (AE, vital signs, ECG and clinical lab safety test) and PK data (up to 24h) for a minimum of 5 participants on active will be reviewed before proceeding to the next dose level.
- A maximum total dose of 2000 μg over a 24 hour period will not be exceeded.

Part B is planned to follow Part A and progression will be based on an acceptable safety, tolerability and pharmacokinetic profiles. The highest well tolerated dose achieved in Part A will be selected for Part B.

- Part B will evaluate the safety, tolerability and pharmacokinetics of repeat doses of GSK2292767 administered as a dry powder. Pharmacodynamic effects on biomarkers will also be assessed.
- Twelve participants will be randomised to receive GSK2292767 or the matching placebo, once daily for 14 consecutive days. Participants will be randomised to active or placebo in a 3:1 ratio.
- On the first day of dosing, only two participants will be dosed for the 14 day period (randomisation schedule designed so that one placebo and one active will be dosed on first day). Following a review of the safety data for the first set of participants and assuming no safety concerns (after completion of the 14 day dosing) the remaining participants will be dosed.

Number of Participants: In Part A for each cohort, a sufficient number of participants will be screened to achieve 16 randomised participants. Participants will be randomised to one of four treatment sequences.

In Part B, a sufficient number of participants will be screened to achieve 12 randomised participants with the aim to achieve approximately 9 completed participants on the active treatment group and 3 on placebo. Participants will be randomised to either GSK2292767 or placebo.

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence/regimen at the discretion of the Sponsor in consultation with the investigator.

Treatment Groups and Duration:

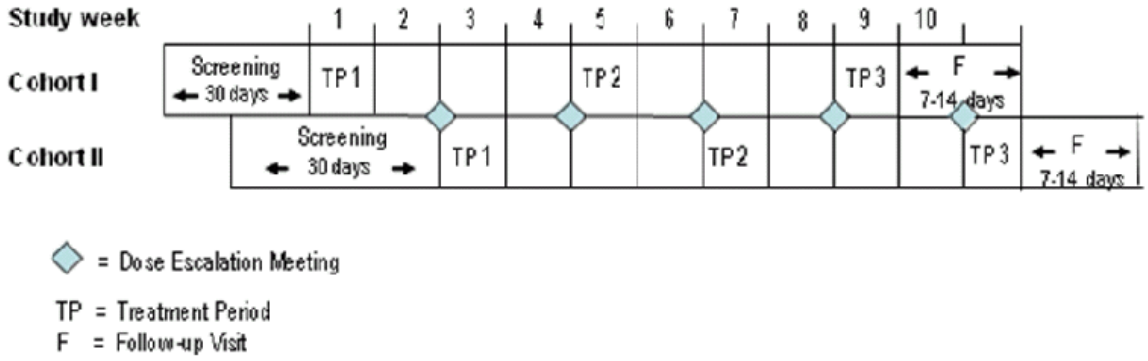
In Part A (cohorts 1 & 2), participants will be randomised to one of 4 treatment sequences. Participants will be randomised such that in each period 12 participants will receive GSK2292767 and 4 participants will receive placebo. Sentinel dosing of the first 2 participants in each period will be performed ensuring one participant will receive the active dose strength and the other on placebo.

In Part B, 9 participants will be randomised to receive the selected dose strength of GSK2292767 and 3 participants will be randomised to receive placebo. The planned dose in Part B is 2000 μg GSK2292767 once daily for 14 days. However, the actual dose will be selected only after review of the safety, tolerability and PK data from Part A. The dose will not exceed 2000 μg GSK2292767 per day. Sentinel dosing of the first 2 participants

will be performed ensuring one participant will receive the active dose strength and the other on placebo for the 14 day treatment period.

Part A: Study Duration

Screening	Within 1 to 30 days prior to the first dose
Treatment Period	Each cohort will be comprised of three treatment periods. During each period, participants will be admitted to the unit the day before dosing and will be discharged after completion of 24h post-dose assessments.
Washout Period	Will be approximately 4 weeks between doses for an individual participant.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.



Part B: Study Duration

Screening	Within 1 to 30 days prior to the first dose
Treatment Period	Will be 14 days. Participants will remain in-house during the entire dosing period and be discharged on Day 15 after completion of all assessments.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

2. SCHEDULE OF ACTIVITIES (SOA)

- The timing and number of planned study assessments, including safety, pharmacokinetic, and pharmacodynamic/biomarker assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments 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 Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed consent form (ICF).

2.1. SOA -Screening

Procedure	Screening (up to 30 days before Day 1)	Notes
Informed consent	X	
Inclusion and exclusion criteria	X	Recheck clinical status before randomisation
Demography	X	
Complete physical examination including height and weight	X	
Medical history (includes substance usage)	X	Substances: Drugs, Alcohol, tobacco and caffeine
Urine Pregnancy test	X	
Human Immunodeficiency Virus (HIV), Hepatitis B and C screening	X	1. If test performed within 3 months prior to first dose of study treatment, testing at screening is not required
Laboratory assessments	X	
12-lead ECG (in triplicate)	X	See Section 9.3.3
Vital signs (in triplicate)	X	See Section 9.3.2
Sputum induction	X	Requires >100mg for inclusion
Spirometry	X	Maximal amount of air forcefully exhaled in 1 second (FEV1) and Forced Vital Capacity (FVC). Perform before sputum induction
Urine Drug, Alcohol and Smoking breath test	X	
24h Holter monitor	X	

2.2. SOA – Part A (Single Dose)

Procedure	Part A (Single Dose) Treatment Period														Notes
	Day -1	Day 1 (time relative to dosing)													
		Pre dose	0h	5m	30m	45m	1h	2h	3h	4h	6h	8h	12h	24h	
Admission to Unit	X														
Urine Drug/Alcohol breath test	X														
Urine Pregnancy test	X														
Brief Physical Exam	X													X	
Laboratory Assessments	X													X	
Meals	X							X						X	See Section 6.3.1
12-lead ECG (single)		X				X				X			X	X	
Vital signs (single)		X			X		X				X		X	X	
Telemetry		←==========													Cardiac telemetry: To start approximately1hr Pre-dose and then continuously for the first 5h post dose.
Spirometry (triplicate)		X					X								

Procedure	**Part A (Single Dose) Treatment Period**													**Notes**
	Day -1	**Day 1 (time relative to dosing)**												
		Pre dose	**0h**	**5m**	**30m**	**45m**	**1h**	**2h**	**3h**	**4h**	**6h**	**8h**	**12h**	**24h**	
Pharmacokinetic and Metabolite Profile Blood Sample		X		X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic Urine Sample		X	←==========												Only for the maximum proposed dose group if escalated up to (2000 µg).
Inhaler Training	X														
Dosing			X												
Sputum induction									X					X	
Adverse Event Review		←==========													
Concomitant Medication Review		←==========													
Discharge														X	

2.3. SOA – Part B (Repeat Dose)

Procedure	Part B (Repeat Dose) Study Day																			Notes
	D -2 or 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 Unit	X																			
Urine Drug/Alcohol	X																			
Urine Pregnancy test	X																			
Brief Physical Exam	X																			
Laboratory Assessments	X		X[1]		X[1]		X[1]		X[1]		X[1]		X[1]		X[1]	X				1. Perform assessment pre dose
Meals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				See Section 6.3.1
12-lead ECG (single)	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X				2. Perform assessments pre dose and at 30 mins post dose.
Vital signs (single)	X	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				3. Perform assessments pre dose.
Spirometry (triplicate)	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]					. 4. Perform assessment pre dose and 1h post dose.
Pharmacokinetic Blood Sample		X[6]	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[6]	X	X[7]	X[7]	X[7]	5. pre-dose and 5 min post dose. 6. pre-dose, 5 mins, 30 mins, 45 mins, 1, 2, 3, 4, 6, 8 and 12h post dose 7. If following Single dose (SD) PK analysis deemed necessary.

Procedure	Part B (Repeat Dose) Study Day																			Notes
	D -2 or 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	
Blood Sample for Metabolic Profiling															X[6]	X	X[7]	X[7]	X[7]	
Urea Blood Sample																X				Collect sample just before bronchoscopy
Inhaler Training	X																			
Dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Sputum induction	X[11]	X[8]											X[9] [10]							8. 3h post dose 9. 3h and 24h 10. Should sputum induction fail or be insufficient at any time point then the participant will be allowed to return 24h later for a further attempt to obtain an adequate sample 11. Should sputum induction fail or be insufficient then the participant will be allowed to return 24h later for a further attempt to obtain an adequate sample. Failure to produce a baseline sample will result in participant withdrawal.
Bronchoscopy																X				
Adverse Event Review		←==========→																		

Procedure	**Part B (Repeat Dose) Study Day**																			**Notes**
	D -2 or 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**	
Concomitant Medication Review		←==========→																		
Discharge																X				

2.4. SOA – Follow-up

Procedure	Follow-up (7-14 days post last study treatment administration)	Notes
Full physical Examination	X	
12-lead ECG	X	
Vital signs	X	
Laboratory assessments	X	
Adverse Event Review	X	
Concomitant Medication Review	X	

3. INTRODUCTION

Phosphoinositide 3 Kinase delta (PI3Kδ) is a lipid kinase expressed predominantly in leucocytes, which converts phosphatidylinositol (4,5)-bisphosphate (PIP2) into Phosphatidylinositol (3,4,5)-trisphosphate (PIP3), a powerful second messenger responsible for activation, proliferation and function of multiple cell types, thereby modulating immune responses [Fung-Leung WP, 2011]. PI3Kδ inhibition will potentially prevent recruitment of inflammatory cells, including T lymphocytes or eosinophils and also inhibits the release of pro-inflammatory mediators from neutrophils such as cytokines, chemokines, reactive oxygen species, and proteolytic enzymes. In addition, targeting the PI3Kδ pathway enhances innate immune responses to infections by promoting neutrophil and T cell mediated host defence. Of interest for the treatment of severe respiratory disease is the observation that inhibition of PI3Kδ may restore steroid effectiveness under conditions of oxidative stress [Okkenhaug, 2002]. An inhaled PI3Kδ inhibitor may be beneficial for both asthma and chronic obstructive pulmonary disease (COPD).

3.1. Asthma

There are a number of immune cell types which contribute to allergen-induced asthma, including T-cells, eosinophils, B-cells and mast cells. In allergic asthma, the pre-dominant subset of effector T-cells, type 2 T helper (Th2) cells produce IL (interleukin)-4, IL-5, IL-9 and IL-13 [Holgat, 2008]. IL-4 promotes the secretion of allergen specific IgE, which activates mast cells to release mediators such as histamines, prostaglandins and leukotrienes, leading to tissue inflammation. Additionally, IL-5 stimulates B-cell growth and immunoglobulin (Ig) secretion as well as being a key mediator of eosinophil activation.

A selective PI3Kδ inhibitor is predicted to block T-cell activation in the lung, reducing the production of pro-inflammatory Th2 cytokines. PI3Kδ is also involved in B-cell and mast cell activation which are key contributors to asthma pathogenesis [Rowan, 2012]. Therefore the inhibition of PI3Kδ should dampen down the inflammatory cascade involved in the asthmatic response through a wide breadth of pharmacology.

A key role for PI3Kδ in asthma is supported by investigations which have followed the generation of p110δ kinase dead knock-in mice [Okkenhaug, 2002]. These studies demonstrated that PI3Kδ is required for cell activation downstream of the T Cell Receptor and B Cell Receptor and the mast cell high-affinity IgE receptor FcεRI [Okkenhaug, 2007]. Functionally, PI3Kδ is required for cytokine production and proliferation in T-cells, for antibody production, including IgE, in B-cells, and for proliferation and migration as well as allergen-IgE-induced degranulation in mast cells [Ali, 2004]. In a Phase1 study of the PI3Kδ inhibitor Idelalisib in grass pollen challenged allergic rhinitis patients, allergic symptoms were reduced after drug treatment, consistent with a mast cell role for PI3Kδ, as were the percentage of ex vivo–activated basophils or the plasma concentrations of the Th2 attracting chemokines CCL17 and CCL22 [Horak, 2016]. The dual PI3Kγ-PI3Kδ inhibitor duvelisib (IPI-145) inhibited key cytokines and chemokines involved in the asthmatic response in a Phase IIa allergen challenge study of patients with mild allergic asthma (NCT01653756). Although the study primary endpoint

of significantly improving the maximum asthmatic response as measured by Maximal amount of air forcefully exhaled in 1 second (FEV1) (a standard lung function test that measures the amount of air that can be exhaled in one second) was not met, multiple secondary efficacy endpoints were significantly positive including an improvement in FEV1 AUC over the entire assessment period ($p = 0.013$) and a decrease in airway hyper-reactivity ($p = 0.036$) [Infinity Pharmaceuticals, 2014].

3.2. COPD

As anti-inflammatory agents, PI3Kδ inhibitors act via mechanisms that are complementary to those of steroids, and it is thus anticipated that they could further reduce the inflammation underlying COPD, in particular through inhibitory effects on the inflammatory actions of neutrophils. Lung extracts or peripheral blood neutrophils isolated from COPD patients have been found to over-express PI3Kδ resulting in increased PI3Kδ activity [To, 2010; Milara, 2014]. Additionally, PI3Kδ activation has been reported to contribute to corticosteroid insensitivity leading to a loss of the anti-inflammatory and immunosuppressive effects of steroids in COPD [Marwick, 2010].

In addition to anti-inflammatory properties, PI3Kδ inhibition improves neutrophil functionality and in particular corrects the aberrant migration directionality which is specifically observed in COPD neutrophils [Walton, 2015]. This aberrant migration could be in part responsible for the wide spread lung tissue damage associated with COPD, along with the high bacterial colonization seen in the lungs of COPD patients. While improvement in neutrophil functionality will result in a more effective anti-bacterial response, PI3Kδ inhibitors may also provide benefits in preventing infections by common airway bacterial pathogens such as S. pneumoniae [Fallah, 2011].

Recently, several inherited activating mutations in human PI3Kδ have been discovered [Angulo, 2013; Lucas, 2015]. Affected individuals have an immunodeficiency disorder with a reduced life expectancy, and suffer from progressive lung damage as a result of recurrent respiratory infections and persistent lung sepsis, caused by bacterial pathogens such as H. influenzae and S. pneumoniae.

3.3. Study Rationale

This study is the first administration of GSK2292767 to humans. The study will evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and repeat inhaled doses of GSK2292767 in healthy smokers. This study is intended to provide sufficient confidence in the safety of the molecule and preliminary information on target engagement to allow progression to further repeat dose and proof of mechanism studies.

3.4. Background

GSK2292767 has a similar pharmacological profile to GSK2269557, which has been administered to healthy participants (smokers and non-smokers), patients with stable COPD; patients experiencing a COPD exacerbation; and patients with persistent, uncontrolled asthma. GSK2292767 has a different chemical structure resulting in differentiated physical chemistry properties.

A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK2292767 is provided in the Investigator's Brochure [GlaxoSmithKline Document Number 2016N281480_00].

3.5. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2292767 may be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2016N281480_00].

3.5.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK2292767]		
Bronchospasm	A general risk with Inhaled treatment	All doses of study treatment will be administered in the clinical pharmacology unit in the presence of trained clinical staff. Spirometry will be conducted pre and post dose. Treat immediately with a short-acting inhaled bronchodilator. GSK2292767 should be discontinued immediately, the participants assessed and, if necessary, an alternative therapy instituted as deemed appropriate by the investigator or the attending physician. Participants will be withdrawn from the study.
Unknown risks to an embryo, fetus or nursing infant	There are no studies with GSK2292767 in pregnant or lactating women.	As specified in the protocol: • Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate. Female participants must be postmenopausal. • If a female participant becomes pregnant during the study, she must let the study doctor know immediately. The study medication will be stopped. Male participants with female partners of reproductive potential must use highly effective

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		contraception methods to avoid pregnancy while in this study.
Study Procedures		
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm	The lowest possible concentration of saline will be used first and the procedure terminated once sufficient sputum has been obtained. Participants will receive a dose of bronchodilator prior to starting the procedure. The procedure will stopped immediately and the participant treated with a short-acting inhaled bronchodilator should bronchospasm occur and a significant reduction in FEV1 (>25% from pre procedure baseline) observed
Bronchoscopy	Sore throat and transient cough can occur following bronchoscopy but are self limiting. Sedation is used for the procedure with associated risks and is with low dose midazolam and Fentanyl. There is a small risk of transient pyrexia that typically occurs within 24 to48-hours of the BAL procedure.	Bronchoscopy/BAL will be performed by an experienced bronchoscopist in accordance with the guidelines published by the British Thoracic Society [Du Rand, 2013] in a dedicated ward area. The use of sedation and local anaesthetics for the bronchoscopy will be according to local practice. Participants will be continuously monitored throughout the procedure for pulse, blood pressure and pulse oximetry. In case of an adverse event following the BAL procedure participants will be kept under observation at the discretion of the investigator and a Respiratory Physician review obtained if indicated.

3.5.2. Overall Benefit Risk Conclusion

The study will be run in a GSK unit with expertise in conducting first time in human studies and with adequate equipment and staff training to manage clinical emergencies. The GSK unit is based in a teaching hospital. Participant enrolment will be limited to otherwise healthy male and female (of non-childbearing potential) cigarette smokers who also agree to adhere to mandated contraception requirements.

In this single and repeat dose study; evidence for adverse events will be monitored closely, both via subjective reporting and by objective means, i.e. serial assessments of vital signs, ECGs and clinical laboratory information. The in-house periods as detailed in the SoA will allow for continuous medical monitoring for all participants following the first dose.

An interlocking cohort dose escalation design will be used for Part A which will ensure approximately fortnightly dose escalations to occur while allowing for a sufficient washout period (see Section 5 for a detailed discussion of the study design). Sentinel dosing will be used at each dose escalation and also for the repeat dose cohort. Dose escalation will only proceed after a blinded review of safety, tolerability and pharmacokinetics obtained in at least 5 active participants at the prior dose level. For further details of the dose escalation and stopping criteria see Section 7.2.

For Part B (the repeat dose component), the intention is to test only one dose. A review meeting will be held after Part A and prior to Part B to review the safety, tolerability and pharmacokinetic data of single doses up to 24 hours. Following review of this data the dose for Part B will be selected and will not exceed 2000 mcg.

Sputum induction will be performed and monitored by suitably trained medical staff.

Bronchoscopy will be performed in Part B to assess airway drug levels. Bronchoscopy will be undertaken by an experienced bronchoscopist in accordance with the guidelines published by the British Thoracic Society [Du Rand, 2013] in a dedicated ward area.

Participants will return to the clinical unit for a follow up safety examination and adverse event reporting 7 to 14 days post the final dose.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	

• To assess the safety and tolerability of single and repeat doses of GSK2292767 as a dry powder in healthy cigarette smokers.	• Safety and tolerability of GSK2292767 as assessed by clinical monitoring of:
	  • Vital Signs
	  • Spirometry
	  • ECG
	  • Laboratory safety data
	  • Adverse events (AEs)

Secondary	
• To determine the pharmacokinetic profile of single and repeat doses of GSK2292767 as a dry powder in healthy cigarette smokers.	• GSK2292767 plasma concentration data and derived pharmacokinetic parameters including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}),terminal half-life ($T_{1/2}$) and trough concentrations ($C\tau$) following single and repeated dry powder doses, where data allow.
• To investigate the steady-state trough concentration of GSK2292767 in lung epithelial lining fluid (ELF) and Bronchoalveolar lavage (BAL) cell pellet after repeat inhaled dry powder administration in healthy cigarette smokers.	• BAL concentrations of GSK2292767 and derived lung ELF and cell pellet deposition parameters.
Exploratory	
• To determine the pharmacodynamic effect of GSK2292767 on the biomarker PIP3 in induced sputum after single and repeat doses of GSK2292767administered as a dry powder in healthy cigarette smokers.	• PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area) in induced sputum cells.
• To explore the intracellular distribution, binding and lysosomal disposition of GSK2292767 from lung resident cells derived from bronchoalveolar lavage at steady-state following repeat administration	• Semi quantitative characterisation of intracellular distribution of GSK2292767 within lung resident cells, binding and lysosomal uptake and retention.

Objective	Endpoint
• To generate samples that will be used to characterise the metabolic profile of GSK2292767 in plasma, following single and repeat doses of GSK2292767 administered as a dry powder in healthy cigarette smokers.	• Characterisation and quantification of metabolites in plasma.
• To collect urine samples only at the highest proposed dose level to characterise the renal excretion of systemically available drug following inhaled delivery.	• Semi-quantitative characterisation of amount of parent GSK2292767 excreted in urine

5. STUDY DESIGN

5.1. Overall Design

This is a two part, single site, randomised, double-blind (sponsor open), placebo controlled study in healthy smokers.

Part A

- Part A will consist of two 3-period interlocking cohorts to evaluate the safety, tolerability and pharmacokinetics of ascending single doses of GSK2292767 administered as a dry powder. Pharmacodynamic effects on biomarkers will also be assessed.
- In each cohort 16 participants will be randomised to one of four treatment sequences. 12 participants will receive placebo in one of the periods, where as four participants will receive the active dose in all periods.
- The planned doses of GSK2292767 for this study are 50, 100, 200, 500, 1000 and 2000 μg, and these may be modified based on review of safety, tolerability and PK data . The two cohorts together are to achieve dose escalation from a low starting dose to a maximum safe and well-tolerated dose.
- On the first day of dosing, only two participants will be dosed (randomisation schedule designed so that one placebo and one active will be dosed on first day). Following review of the safety data for the first set of participants, and assuming no safety concerns, the remaining participants will be dosed.
- Following each dose level, safety data (AE, vital signs, ECG and clinical lab safety test) and PK data (up to 24h) for a minimum of 5 participants on active will be reviewed before proceeding to the next dose level.
- A maximum total dose of 2000 μg over a 24 hour period will not be exceeded.

Part B is planned to follow Part A and progression will be based on an acceptable safety, tolerability and pharmacokinetic profile. The selection of an appropriate dose for Part B

will be performed upon consideration of available safety and tolerability and PK data from Part A.

The highest well tolerated dose achieved in Part A will be selected for Part B. Part A participants will be considered for Part B, with a washout period of at least 2 weeks between doses for an individual participant. These participants will be re-screened as detailed in the SoA with the exception of the sputum induction procedure.

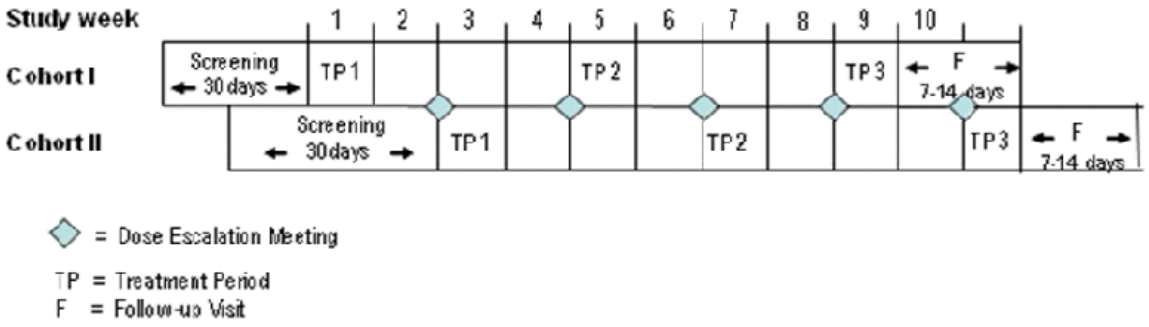
Part B

- Part B will evaluate the safety, tolerability and pharmacokinetics of repeat doses of GSK2292767 administered as a dry powder. Pharmacodynamic effects on biomarkers will also be assessed.
- Twelve participants will be randomised to receive GSK2292767 or the matching placebo, once daily for 14 consecutive days. Participants will be randomised to active or placebo in a 3:1 ratio.
- The total daily dose will not exceed doses that are considered to be well tolerated in Part A.
- On the first day of dosing, only two participants will be dosed for the 14 day period (randomisation schedule designed so that one placebo and one active will be dosed on first day). Following a review of the safety data for the first set of participants (after completion of the 14 day dosing) the remaining participants will be dosed.

Study medication will be administered in a fasted state for all parts of the study.

Part A: Study Duration

Screening	Within 1 to 30 days prior to the first dose
Treatment Period	Each cohort will be comprised of three treatment periods. During each period, participants will be admitted to the unit the day before dosing and will be discharged after completion of 24h post-dose assessments.
Washout Period	Will be approximately 4 weeks between doses for an individual participant
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.



Part B: Study Duration

Screening	Within 1 to 30 days prior to the first dose
Treatment Period	Will be 14 days. Participants will remain in-house during the entire dosing period and be discharged on Day 15 after completion of all assessments.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

5.2. Number of Participants

In Part A for each cohort, a sufficient number of participants will be screened to achieve 16 randomised participants. Participants will be randomised to one of four treatment sequences as detailed in Section 7.3.

In Part B, a sufficient number of participants will be screened to achieve 12 randomised participants with the aim to achieve approximately 9 completed participants on the active treatment group and 3 on placebo. Participants will be randomised to either GSK2292767 or placebo as detailed in Section 7.3.

If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence/regimen at the discretion of the Sponsor in consultation with the investigator.

5.3. Participant and Study Completion

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

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

5.4. Scientific Rationale for Study Design

The study design has addressed regulatory recommendations for First Time in Human (FTIH) studies and preclinical findings for GSK2292767, contributing to the frequency, type and duration of safety assessment and monitoring during treatment periods. This study will include placebo control within each treatment period to allow for a valid evaluation of adverse events attributable to treatment versus those independent of treatment.

This study will recruit healthy smokers to remain consistent with previous studies, and increase the likelihood of obtaining sputum samples.

Part A will be utilising placebo replacement, and the interlocking design has been set-up such that dose escalations are able to occur approximately every 2 weeks and participants approximately have a 4 week wash out period between treatment periods. This will allow for any adjustment needed based on emerging safety, tolerability and pharmacokinetic

information, and sufficient time between doses to eliminate most if not all the drug from the previous dose.

As this is a FTIH study, the doses in Part A will be staggered and participants will be divided into several groups. On Day 1 of each treatment period two participants will be dosed, 1 on active and 1 on placebo. Assuming adequate clinical safety from the Day 1 participants, the remaining 14 participants will be subsequently dosed in staggered groups.

Dose escalation decisions, including the definition of the next dose, will be made by the GSK Study Team with agreement of the Principal Investigator or delegate, based upon review of safety and available PK data from the previous dose(s). The Principal Investigator or delegate and other relevant clinical staff will attend the first part of each review meeting to update the GSK Study Team on clinical observations from the previous dose level and to participate in the blinded data review. The review data set will at minimum consist of the listings of any adverse events, liver function test results, flagged vital signs, ECG and laboratory findings, and PK results derived from 24 hour plasma profiles.

Initial dosing in Part B will not commence until results from Part A have been fully reviewed.

On Day 1, two participants will be dosed; 1 on active and 1 on placebo. Assuming adequate safety upon completion at Day 15, the remaining 10 participants will be subsequently dosed in staggered groups. In addition for Part B additional blood samples may be taken at 48, 72 and 96 hours post Day 14 dose to adequately assess the terminal elimination rate from plasma of GSK2292767. The preliminary PK data for the dose escalation process will be used and the decision documented within this communication to the site at the end of Part A and before the commencement and selection of the dose for Part B.

Measurement of pharmacodynamic (PD) endpoints for the effects of GSK2292767 on PI3Kδ and its downstream pathway has the potential to provide information on the level of target engagement. This should help guide appropriate pharmacodynamic assessments and possibly determine dose selection for subsequent studies in participants with active PI3Kδ pharmacology.

5.5. Dose Justification

To support dose selection for the proposed study, predictions for the effects of GSK2292767 are based on observed pharmacokinetic (PK) and pharmacodynamic (PD) data in rats (systemic and lung), *in vitro* metabolism in rats and *in vitro* PD assessments in human tissues and cell lines. The assumptions made in the development of the model to predict systemic exposure and lung deposition are described in the section below.

GSK2292767 is likely to have moderate volume of distribution in human, a moderate-high plasma clearance (12 to 15 mL/min/kg) and a moderate terminal half-life (11h). Oral bioavailability is likely to be low (as for the rat) suggesting that systemic exposure will result predominantly from the fraction directly absorbed from the lung.

GSK2292767 plasma concentration profiles at steady-state in human were predicted from the compartmental analysis of the rat data. Human exposure predictions are based on this extrapolation and a number of assumptions, taking a conservative approach were possible, are detailed as follows:

- Lung deposition as a ratio of the amount swallowed is expected to be 1:4 (or 80% swallowed of the delivered dose)
- Instant dissolution of the dry powder (making drug more available for appearance in plasma)
- Complete and rapid absorption across the lungs
- No attributable oral absorption and contribution to systemic exposure from swallowed fraction
- Same drug distribution (volume of distribution, Vd) in human as in rat
- Human clearance scaled from rat using standard allometry
- Linear pharmacokinetics across dose range 50 to 2000 µg
- No appreciable (not greater than 2-fold) accumulation on repeat administration

The following table below contains the output of this simulation for the predicted systemic exposures (for C_{max} and AUC_{24}) for the proposed dose range in this study:

Table 1 Predicted human systemic PK exposure (plasma) following single doses of GSK2292767

Nominal Dose[1] (µg)	Predicted[2] AUC (0-24) (ng.h/mL)	Predicted[2] Cmax (ng/mL)
50	0.125	0.075
100	0.25	0.15
200	0.5	0.3
500	1.25	0.75
1000	2.5	1.5
2000	5	3

1. Amount of GSK2292767 in Ellipta™ device
2. Prediction based on the maximum possible 20% of nominal dose deposited in lungs and then being systemically available

These predicted exposures represent the most likely systemic exposure in human based on the available data and knowledge of inhaled dry powders. However to generate the most conservative exposure estimate to humans against the non clinical toxicology data and toxicokinetic parameters a 100% lung deposition with 100% bioavailability (as opposed to the approximate 20% which is typical for an inhaled dry powder estimate) has been used to generate the following Table 2 which shows the relative margins against both rat and dog 13 week GLP studies.

Table 2 Human safety margins based on the predicted maximum systemic exposures (plasma) following a single inhaled administration of GSK2292767 to healthy volunteers via Ellipta™ compared to the NOAEL exposures from rat and dog toxicology studies.

Dose (μg)[1]	Steady-state $AUC_{(0-24)}$ (ng.h/mL)		Steady-state C_{max} (ng/mL)		Lung Concentrations (ng/g)[5]	
	Rat[2]	Dog[3]	Rat[2]	Dog[3]	Rat[2]	Dog[3]
	Safety cover multiple[4]		Safety cover multiple[4]		Safety cover multiple[4]	
50	208	473	115	191	757	1342
100	104	240	58	96	379	671
200	52	120	28	48	189	336
500	21	47	12	19	76	134
1000	10	24	6	10	38	67
2000	5	12	3	5	19	34

1. Nominal Ellipta™ dose
2. Based on rat day 13 week GLP tox data (males and females combined) at 3240 μg/kg/day with a No Observed Adverse Effect Level (NOAEL) exposure of 43.3 ng/mL and 130 ng.h/mL for Cmax and AUC respectively.
3. Based on dog day 13 week GLP tox data (males and females combined) at 2950 μg/kg/day with a NOAEL exposure of 71.5 ng/mL and 296 ng.h/mL for Cmax and AUC respectively.
4. Assuming 100% of the delivered dose is bioavailable in human
5. Assuming 7 or 25% of delivered dose in tox studies is deposited in the lungs and lung weights of 6 or 11 g/kg for rat and dog respectively. Human lung weight is 14.3 g/kg (based on 70kg body weight and the maximum possible deposition is used for multiples of 100% of nominal dose)

5.5.1. Starting dose and maximum dose justification

The dose justification for this PI3Kδ asset is guided by not only our understanding of the pre-clinical testing of GSK2292767 but also specifically in terms of target pharmacology information from another GSK PI3Kδ asset GSK2269557 has also been used. GSK2269557 has so far been administered once daily to healthy volunteers, COPD patients (both mild/moderate and exacerbating populations) as well as asthmatics. Healthy volunteers have received doses up to 6400 μg via nebulisation, 3000 μg via dry powder for up to 14 days and mild/moderate COPD patients have received maximum doses of 2000 μg up to 14 days and exacerbating COPD patients at 1000 μg doses for 3 months.

Achieved steady-state plasma exposures at 2000 μg in the 14 day study in healthy volunteers achieved an approximate maximum 44% inhibition of PI3Kδ by day 7. Based on lung lavage data and intracellular effect compartment concentrations of GSK2269557 the estimated PI3Kδ inhibition in this study was approximately ≥ 95% by Day 7.

The starting dose of 50 μg is expected to result in at worst (100% systemic exposure) a level of systemic exposure in humans that would be at least 100-fold lower than the level of exposure deemed as the NOAEL in toxicology species. The predicted C_{max} at 50 μg would only be expected to give a maximum PI3Kδ inhibition of approximately 10%.

The maximum dose of 2000 µg is expected to result in at worst (100% systemic exposure) a level of plasma exposure in humans that would be in the range of 3-12-fold lower than the level of exposure deemed as the NOAEL in toxicology species. The predicted C_{max} at 2000 µg would give a maximum PI3Kδ inhibition of approximately 81%.

In terms of topical lung exposure in humans to GSK2292767 this molecule has not been in human before and therefore the standard assessment of deposition to the lungs is used, using a conservative estimate of 100% for human, as well as relevant toxicology information. The minimum lung safety cover based on the maximum proposed dose is approximately 19-fold based on the rat data. This is higher than the standard 10-fold minimum safety margin for an unmonitorable finding in toxicology for which there was NO such finding for GSK2292767.

The systemic exposure will be assessed at each dose level whilst the trial is being conducted using the blinded nominal time data to review and update the predictions using actual data in particular to make predictions for the higher dose levels in Part A as well as the Part B repeat dose phase. Please see Section 7.2 for dose adjustment details.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including (medical history, physical examination, laboratory tests, and cardiac monitoring). A participant with a clinical abnormality or laboratory parameters outside the reference range expected for them and the population being studied may be included only if the Investigator believes that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures or outcomes.
3. Participants who are current daily cigarette smokers (manufactured and self-rolled). Must have smoked regularly in the 12-month period preceding the screening visit.
4. Normal spirometry (FEV1 ≥80% of predicted) at screening. Predictions will be based upon [Quanjer, 2012].

Weight

5. Body weight ≥50kg and body mass index (BMI) within the range 18 to 31 kg/m2 (inclusive).

Sex

6. Male and female

a. Male participants:

A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least from the time of first dose of study medication until at least 55 (5x11) hours plus an additional 90 days after the last dose of study medication and refrain from donating sperm during this period. GSK2292767 has a predicted half-life of approximately 11 hours.

b. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and:

(i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data
2. Abnormal blood pressure as determined by the investigator
3. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
4. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
6. Average QTcF >450 msec (based on triplicate ECGs)

NOTES:

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

7. Participants who have asthma or a history of asthma (except in childhood and which has now remitted).

Prior/Concomitant Therapy

8. Past or intended use of over-the-counter or prescription medication including herbal medications within 14 days prior to dosing. Specific medications listed in Section 7.7 may be allowed.
9. Live vaccine(s) within 1 month prior to screening, or plans to receive such vaccines during the study

Prior/Concurrent Clinical Study Experience

10. Participation in the 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 prior to the first dosing day
12. Current enrolment or past participation within the last 90 days of exposure to any other clinical study involving an investigational study treatment or any other type of medical research

Diagnostic assessments

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

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

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

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

15. Positive pre-study drug/alcohol screen
16. Positive human immunodeficiency virus (HIV) antibody test
17. Regular use of known drugs of abuse

Other Exclusions

18. Regular alcohol consumption within 3 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.
19. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study
20. Participants who are unable to produce a total weight of at least 100 mg of selected sputum during sputum induction at screening.
21. Participants whose primary consumption of tobacco is via methods other than cigarettes (manufactured or self-rolled). Primary methods of tobacco consumption that are excluded include, but are not limited to pipes and cigars.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids from 7 days before the start of study treatment until after the final dose.

- In all Parts, on all dosing days, participants will be required to fast from at least 2 hours before drug administration and until 2 hours after administration of study treatment. At other times, snacks and meals will be provided by the clinical unit. Water will be allowed as desired except for 2 hours before and 2 hours after drug administration.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 6 hours before the start of dosing until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- Smoking is permitted during the study, whilst resident in the unit participants will be escorted to a designated smoking area.

6.3.3. Activity

- Participants will abstain from strenuous exercise for a minimum of 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. 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, and any serious adverse events (SAEs).

Individuals who were reserved and not subsequently dosed and 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.

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatment Name:	GSK2292767 ELLIPTA™ Drug Powder Inhaler (DPI) (50 µg)	GSK2292767 ELLIPTA™ DPI (500 µg)	Placebo ELLIPTA™ DPI
Formulation description:	GSK2292767 blended with lactose and magnesium stearate	GSK2292767 blended with lactose and magnesium stearate	Lactose
Dosage formulation:	DPI	DPI	DPI
Unit dose strength(s)/Dosage level(s):	50 µg per blister X µg / blister	500 µg per blister	N/A
Route of Administration	Inhaled	Inhaled	Inhaled
Dosing instructions:	Inhale as directed	Inhale as directed	Inhale as directed
Method for individualizing dosage:	DPI containing a single strip with 30 blisters	DPI containing a single strip with 30 blisters	DPI containing a single strip with 30 blisters
Packaging and Labeling Do not include a sample of the label text or details of pack design in the protocol.	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.	Study Treatment will be labelled as required per country requirement.
Manufacturer	GSK	GSK	GSK

7.2. 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 2000 µg (nominal) GSK2292767 and the maximum daily exposure of GSK2292767 is not intended to exceed the steady-state exposure at the NOAEL in the 13 week rat toxicology studies ($AUC_{(0\text{-}24h)}$ 130 ng.h/mL; C_{max} 43.3 ng/mL).

The following dose adjustment/PK stopping criteria will be employed:

- If exposure in a participant reaches or is predicted to reach 130 ng.h/mL for $AUC_{(0\text{-}24h)}$ and/or 43.3 ng/mL for C_{max}, the participant will be withdrawn from the study.

- If mean group exposure reaches or is predicted to reach 130 ng.h/mL for $AUC_{(0-24h)}$ and/or 43.3 ng/mL for C_{max}, dose escalation will be stopped.

If 3 or more participants withdraw based on PK stopping criteria, dose escalation will be temporarily halted and no further participants will be dosed until review of all the data has taken place.

7.3. Method of Treatment Assignment

Study using Pre-Coded Randomisation provided to site	On Day 1, participants will be assigned a unique number (randomisation number) in ascending numerical order at each study site. The randomisation number encodes the participant's assignment to one of the treatment sequences (Part A) or treatment arms (Part B) of the study, according to the randomisation schedule generated prior to the study by the Clinical Statistics Department at GSK. Each participant will be dispensed blinded study treatment, labelled with their unique randomisation number, throughout the study. Once a randomisation number has been assigned, it must not be reassigned.

7.3.1. Part A

In Cohorts 1 & 2, participants will be randomised to one of 4 treatment sequences as described in Table 3. Participants will be randomised such that in each period 12 participants will receive GSK2292767 and 4 participants will receive placebo. Sentinel dosing of the first 2 participants in each period will be performed ensuring one participants will receive the active dose strength and the other on placebo. No participant will be a sentinel participant on more than one occasion.

Table 3 Part A: Treatment Sequences

1	1	4	Placebo	Dose Level 3	Dose Level 5
	2	4	Dose Level 1	Placebo	Dose Level 5
	3	4	Dose Level 1	Dose Level 3	Placebo
	4	4	Dose Level 1	Dose Level 3	Dose Level 5
2	5	4	Placebo	Dose Level 4	Dose Level 6
	6	4	Dose Level 2	Placebo	Dose Level 6
	7	4	Dose Level 2	Dose Level 4	Placebo
	8	4	Dose Level 2	Dose Level 4	Dose Level 6

The planned treatments are as indicated in Table 4:

Table 4 Part A: Planned Treatments

Treatment	Dose Level	Description (Planned dose level)
A	Placebo	Placebo inhaled single dose
B	Dose Level 1	50 μg GSK2292767 inhaled single dose
C	Dose Level 2	100 μg GSK2292767 inhaled single dose
D	Dose Level 3	200 μg GSK2292767 inhaled single dose
E	Dose Level 4	500 μg GSK2292767 inhaled single dose
F	Dose Level 5	1000 μg GSK2292767 inhaled single dose
G	Dose Level 6	2000 μg GSK2292767 inhaled single dose

1. Note: Doses may be modified based on emerging data.

7.3.2. Part B

Nine participants will be randomised to receive the selected dose strength of GSK2292767 and 3 participants will be randomised to receive placebo. The planned dose in Part B is 2000 μg GSK2292767 once daily for 14 days. However, the actual dose will be selected only after review of the safety, tolerability and PK data from Part A. The dose will not exceed 2000 μg GSK2292767 per day. Sentinel dosing of the first 2 participants will be performed ensuring one participant will receive the active dose strength and the other on placebo for the 14 day treatment period.

Table 5 Part B Planned Treatments

Treatment	Dose Level	Description (Planned dose level)
H	Placebo	Placebo inhaled repeat dose
I	Dose Level 7	2000 μg GSK2292767 inhaled repeat dose

1. Note: Dose may be modified based on emerging data.

7.4. Blinding

Blind Break (Envelopes)	A sealed envelope that contains the study treatment assignment for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. GSK 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 (eg, antidote is available). In this case, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the GSK.
Blinded study with unblinded site pharmacy staff who are labelling and ensuring release of the study drug	In Part A participants will be randomised to one of four treatment sequences, and in Part B participants will be randomised in a [3:1] ratio to receive study treatment. Investigators will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, unblinded site pharmacy staff will be responsible for labelling and ensuring release of the blinded study treatment to the investigator or designee. 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(s) 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 Case Report Form (CRF).

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- When participants are dosed at the site, they will receive study treatment 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 treatment 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 treatment.

7.7. Concomitant Therapy

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

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

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

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because the safety and efficacy of GSK2292767has not yet been defined.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Pharmacokinetic Stopping Criteria

This protocol allows some alteration from the currently outlined dosing schedule, please refer to Section 7.2 for more details.

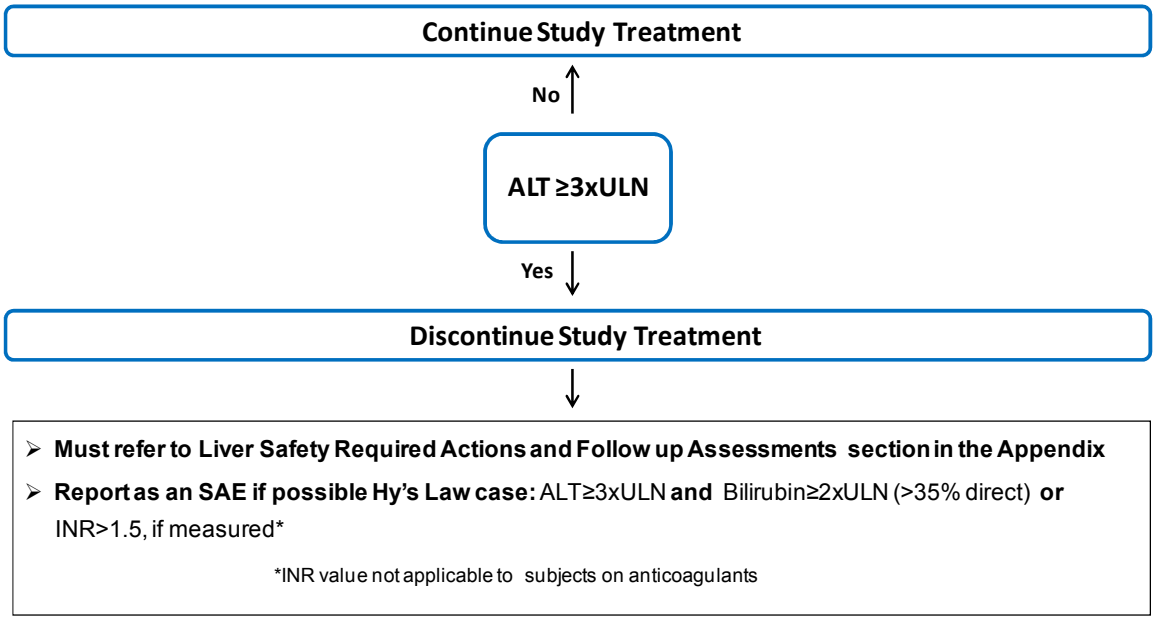
8.1.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

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

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

8.1.3. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
    - For example, if a participant is eligible for the protocol based on QTcF, then QTcF must be used for discontinuation of this individual participant as well.
    - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

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

- QTcF >500 msec,
- Increase from baseline: QTcF >60 msec

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

8.1.4. Safety Stopping Criteria

Dose escalation stopping criteria include the following:

- A serious adverse event (SAE) occurring in 1 or more participants receiving GSK2292767 that is considered at least possibly related to study drug;
- Two or more severe adverse events occurring in a group of participants receiving GSK2292767 that are considered at least possibly related to study drug.

8.1.5. Temporary Discontinuation

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

8.1.6. Rechallenge

8.1.6.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- 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.
- Refer to the SoA for data to be collected at follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. 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 treatment.
- 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 (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
    - The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
    - If assessments are scheduled for the same nominal time, THEN the assessments *should* occur in the following order:
        1. pregnancy test
        2. physical examinations
        3. vital signs
        4. 12-lead ECG
        5. lung function tests (spirometry)
        6. blood draws
        7. sputum induction

      Note: The timing of the assessments must allow the blood draw to occur at the exact nominal time.
    - The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
    - The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the

relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.

- The institutional review board (IRB)/ Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

9.1. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the start of treatment until [the follow-up visit] at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.1.2. 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.

9.1.3. 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 8.3). Further information on follow-up procedures is given in Appendix 4.

9.1.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.1.5. Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until 7 days after the last dose.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

For this study, any dose of GSK2292767 greater than 2000 µg within a 24-hour time period ± 2 hour will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 3 days).
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment 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.

9.3. Safety Assessments

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

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded (at screening only).
- A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.3.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed semi supine with a completely automated device. Manual techniques will be used only if an automated device is not available or in the case of an emergency.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured (triplicate at screening) in a semi-supine position after 5 minutes rest and will include temperature (single reading), systolic and diastolic blood pressure, and pulse (recorded at intervals of no more than 2-5 minutes apart). The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.

9.3.3. Electrocardiograms

- Triplicate/Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTFc intervals. Refer to Section 8.1.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 to 5 minutes apart.

9.3.4. Spirometry

- The maximal amount of air forcefully exhaled in 1 second (FEV1) and forced vital capacity (FVC) will be measured using a spirometer at the time indicated in the SoA.
- All sites will use their existing spirometry equipment.
- FEV1 and FVC measurements will be repeated until three technically acceptable measurements (within 150 mL of each other) have been made. Only the best 3 measurements will be recorded in the eCRF.
- A full description of the timing and conduct of spirometry procedures will be provided in the SRM.

9.3.5. Cardiac Telemetry

- Continuous cardiac telemetry will be performed in Part A, from approximately 1 hr pre-dose to 5 hours post dosing in each period. Full disclosures will be maintained as part of the participant's source documents and will be reviewed in detail.
- Cardiac telemetry might also be done in Part B depending on emerging data (lead II real-time display ECG monitoring is acceptable).

9.3.6. Holter Monitoring

- Holter monitoring will be performed in Parts A & B at screening only. (3 lead holter monitoring is acceptable) for the duration of 24hrs.

9.3.7. Bronchoscopy

- Bronchoscopy assessments will be performed as described in the SoA table.
- Standard procedures for the bronchoscopy assessments described in full in the SRM.
- Bronchial alveolar lavage (BAL) will be collected at bronchoscopy.
- BAL samples for GSK2292767 and urea analysis will be collected at the time points listed in the SoA.
- Details of BAL sample collection, processing, storage and shipping procedures are provided in the SRM.
- GSK2292767 concentration in BAL will need to be corrected for dilution using urea concentration as a correction factor. Consequently a plasma sample taken as soon as practically possible before the BAL samples will be used to determine both plasma and BAL urea concentrations in order to determine the dilution factor.

9.3.8. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or at follow-up should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.4. Pharmacokinetics

- Whole blood samples of approximately 3mL will be collected for measurement of plasma concentrations of GSK2292767 as specified in the SoA. 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 will be used to measure GSK2292767 for PK analysis and to evaluate for the presence of drug-related metabolites. Drug-related metabolites will only be assessed at the top dose level in Part A (single dose phase). Each plasma sample will be divided into 2 aliquots (1 each for PK and metabolite analysis). Urine will also be collected only from the maximum proposed dose group if escalated up to (2000 µg) for semi quantitative assessment of the contribution of the kidney in renal elimination if possible based on detection. Samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Plasma and BAL analysis of GSK2292767 will be performed under the management of the Bioanalysis, Immunogenicity and Biomarkers department, GlaxoSmithKline. Concentrations of GSK2292767 will be determined in all samples using the currently approved analytical methodology. Metabolite analysis and a semi-quantitative assessment of unchanged drug in urine will be performed under the management of the Analytical Sciences & Development department,

GlaxoSmithKline and the results will reported under a separate protocol. All raw data will be stored in the GLP Archives, GlaxoSmithKline.

- BAL cells will be investigated further if possible (depending on cell amount obtained and cell health) for cellular uptake, distribution and binding of GSK2292767. Priority will be given to BAL analysis of GSK2292767 and cell pellet deposition parameters. This work if possible will be conducted under the management of the Platform Technology and Science (PTS) department within GlaxoSmithKline and documented and reported out within the main study outputs.
- Further information on collection, processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

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

9.5. Pharmacodynamics

Pharmacodynamic parameters evaluated in this study are detailed in Section 9.5.

9.6. Genetics

Genetics are not evaluated in this study.

9.7. Biomarkers

9.7.1. Induced Sputum

- Saline induced sputum samples will be captured at all of the time points shown in the SoA.
- The sputum induction process will follow local standard procedures in the presence of a trained physician.
- At screening no analysis of the sputum sample is required, only the weight of the sputum sample is required to confirm that the participant is able to produce an adequate induced sputum sample (>100 mg).
- In Parts A and B samples will be processed and analysed for the detection of PIP2 and PIP3 levels at all time points.
- Further information on collection, processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

9.8. Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

Part A

The sample size of 16 participants per cohort for the single dose, dose escalation (cohorts 1 and 2), is based on feasibility and is deemed an adequate number to provide a preliminary assessment of PK and safety prior to progression into the repeat dose cohort. However, to illustrate the level of precision that could be expected, a sample size calculation has been performed based on PIP3 data collected from GSK2269557 studies.

In PII115117 [GlaxoSmithKline Document Number 2011N124265_00] Part C Cohort 4, between and within participant variances for PIP3 (as a proportion of PIP2 and PIP3) at 3 hours post dose were estimated to be 0.045 and 0.034 respectively on the log scale. Applying these estimates to the design of Part A yields a predicted treatment comparison standard error of each active dose to placebo of approximately 0.1140 on a log scale. This would enable half widths of the 95% confidence interval (CI). to be achieved of ± 0.1898 on the log scale which translates to (-17%, 21%) assuming no difference between treatments for the comparison of PIP3 proportion of each active dose over placebo. Assuming a smaller PIP3 proportion, standard error on a logged scale of 0.071 (as observed in PII116617 Parts B and C combined), the half-widths of the 95% CI would reduce to ± 0.1182 on the log-scale which translates to (-11%, 13%) assuming no difference between treatments.

Part B:

It is anticipated that a sufficient number of participants will be enrolled in the study such that data are obtained from 12 participants (9 participants on active and 3 on placebo). These numbers; together with the participants in Part A, are deemed adequate in order to provide a preliminary assessment of safety and PK prior to progression into longer duration studies However, to illustrate the level of precision that could be expected, a sample size calculation has been performed based on PIP3 data collected from GSK2269557 studies.

In PII116617 [GlaxoSmithKline Document Number 2013N183586_00] Part B, the between participant standard deviation of the differences in treatments of change from baseline at Day 1 3H was estimated to be 0.187 on the log scale. Using this as the estimate along with the study design for Part B, this would enable half widths of the 95% C.I. to be achieved of ± 0.2283 on the log scale which translates to (-20%, 26%) assuming no difference between treatments for the comparison of PIP3 proportion of active dose over placebo.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who were screened
Safety	All randomised participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
Pharmacokinetics	Participants in the 'All participant' population for whom a pharmacokinetic sample was obtained and analysed.

10.3. Statistical Analyses

Statistical analysis will be performed by, or under the direct auspices of Clinical Statistics, GlaxoSmithKline.

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

10.3.1. Safety Analyses

All safety analyses will be performed on the Safety Population.Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

10.3.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modelling and Simulation (CPMS) department within GlaxoSmithKline. Plasma GSK2292767 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, as data permit: maximum observed plasma concentration (C_{max}), time to Cmax (T_{max}), area under the plasma concentration-time curve [$AUC_{(0-t)}$, $AUC_{(0-24)}$, and $AUC_{(0-\infty)}$], concentration at trough (Ctrough is the sample with the lowest concentration which will be immediately before the next day's dose) and apparent terminal phase half-life ($t_{½}$).

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarised descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Respiratory Clinical Statistics, GlaxoSmithKline.

10.3.2.1. Dose Proportionality, for Part A

A preliminary analysis will be conducted to assess the dose proportionality of loge-transformed parameters $AUC_{(0-t)}$, Ctrough and C_{max}, using the power model. If the power model indicates deviations from dose proportionality, further analyses may be performed using the Analysis of Variance (ANOVA) method.

10.3.2.2. Dose Accumulation, for Part B

A preliminary assessment of dose accumulation of GSK2292767 will be made on $AUC_{(0-24)}$, Ctrough and C_{max}. Point estimates and 90% Confidence Intervals will be generated for the difference between the PK parameters for Day 1 and Day 14.

10.3.2.3. Steady State, for Part B

Attainment of steady state will be assessed separately for each cohort through the visual inspection of individual Cmax and Ctrough values plotted over time.

10.3.2.4. Peak to Trough Ratio

Peak to trough ratio will be calculated on each study day as the concentration 5 minutes after dosing divided by the Ctrough concentration on that study day. Peak to trough concentrations will be plotted over time. A longitudinal model may be fitted to explore the change in ratio over time.

10.3.3. Other Analyses

Pharmacodynamic, and biomarker exploratory analyses will be described in the reporting and analysis plan.

10.3.4. Interim Analyses

No formal statistical analysis is planned.

A review of preliminary safety and pharmacokinetic data will be conducted prior to dose escalating within Part A and before confirmation of the dose for Part B. Safety data will be provided by the site at the end of each dosing session. Preliminary analysis of the PK data will be performed using nominal time information to justify the taking of additional blood samples in Part B at 48, 72 and 96 hours post Day 14 dose. If the half-life cannot be adequately determined from a 24 hour sampling regimen then these additional samples will be taken and documented in the dose escalation report before the commencement of Part B. Pharmacokinetic data will be provided by or under the auspices of Clinical Pharmacokinetics Modelling & Simulation (CPMS).

Pharmacodynamic data will be analysed on an ongoing basis as the data become available.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

µg	Microgram
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
ALT	Alanine Aminotransferase
ALT	Alanine Transaminase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Drug Concentration versus Time Curve
AUC(0-t)	Area Under the Plasma Drug Concentration versus Time Curve from zero to time t
AUC(0-24)	Area Under the Plasma Drug Concentration versus Time Curve from zero to 24 hours
AUC(0-∞)	Area Under the Plasma Drug Concentration versus Time Curve from zero to infinity
BAL	Bronchoalveolar Lavage
BMI	Body Mass Index
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
C_{max}	Maximum Observed Plasma Drug Concentration
COPD	Chronic Obstructive Pulmonary Disease
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacokinetics Modelling and Simulation
CRF	Case Report Form
CV	Cardiovascular
DPI	Drug Powder Inhaler
ECG	Electrocardiogram
eCRF	electronic case report form
ELF	Epithelial Lining Fluid
FDA	Food and Drug Administration
FEV1	Maximal amount of air forcefully exhaled in 1 second
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
FVC	Forced Vital Capacity
g	Gram
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
H	hour
hCG	Human chorionic gonadotropin
HBsAg	Hepatitis B surface antigen

H. influenzae	Haemophilus influenzae
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HRT	Hormonal Replacement Therapy
IB	Investigator Brochure
ICF	Informed Consent Form
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
Kg	Kilogram
LDH	Lactate dehydrogenase
mcg	Microgram
mg	Milligram
mins	Minutes
mL	Milliliter
msec	Milliseconds
MSDS	Material Safety Data Sheet
ng	Nanogram
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamic
PI3Kδ	Phosphoinositide 3 Kinase delta
PIP2	Phosphatidylinositol (4,5)-bisphosphate
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PK	Pharmacokinetic
PT	Prothrombin Time
PTS	Platform Technology and Science
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RNA	Ribonucleic Acid
SAEs	Serious Adverse Events
SD	Single dose
SDA	Source Document Agreement
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOA	Schedule of Activities
S. pneumoniae	Streptococcus pneumoniae

SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Terminal Half-life
Th2	Type 2 T helper
T_{max}	Time to Maximum Observed Plasma Drug Concentration
$C\tau$	Trough concentrations
ULN	Upper Limit of Normal
Vd	Volume of distribution
WOCBP	Woman Of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 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 6 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit Activated partial thromboplastin time (aPTT)[3] Prothrombin time (PT)[3]	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	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 fasting (screening only)/ non fasting	Calcium	Alkaline phosphatase	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines). Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] Serology (Human Immunodeficiency Virus (HIV) antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

Laboratory Assessments	Parameters
	The results of each test must be entered into the CRF.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Section 12.6 (Appendix 6) All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
3. Part B (Screening) only.

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

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

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.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion 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.

Source Documents

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

Study and Site Closure

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

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

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

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

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

Definition of SAE

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

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

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 detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent

one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

Recording AE and SAE

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently 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 treatment 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 treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

Reporting of SAE to GSK

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit

this information to the SAE coordinator.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SRM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 7 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
- Refrain from donating sperm for duration of study and for at least 55 hours plus an additional 90 days after the last dose of drug.

Female participants

Table 7 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
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 drug. 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.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed and assayed in a certified laboratory in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

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

Phase I liver chemistry stopping criteria and required follow up assessments

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

If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

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

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended

If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</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 [3days insert time interval recommended by clinical pharmacokinetics representative] of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR</td></tr>
</table>

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	**>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 participants 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 treatment for that participant if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment 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.

12.7. Appendix 7: Protocol Amendment History

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