TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).

Compound Number: GSK2269557

Development Phase: IIA

Effective Date: 22-MAR-2017

Protocol Amendment Number: 04

Author (s): PPD (CCSE); PPD (CPSSO); PPD (Respiratory CEDD); PPD (Exp Biology); PPD (Clinical Statistics); PPD (CPMS); PPD (GCSP).

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N218070_00	2015-JUN-04	Original
2014N218070_01	2015-NOV-30	Amendment No. 1
Remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria and in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. It therefore is not valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.		
2014N218070_02	2016-JAN-26	Amendment No. 2
Increase the body mass index (BMI) range in the inclusion criteria from 18-32 kg/m^2 (inclusive) to 16- 35 kg/m^2 (inclusive). The original BMI range from 18-32 kg/m^2 is a typical range used in both healthy volunteer studies and general subject populations. The revised range is more appropriate for a COPD patient population.		
2014N218070_03	2016-NOV-16	Amendment No. 3
To remove photo toxicity from the protocol and to include minor administrative and clarification changes.		
2014N218070_04	2017-MAR-22	Amendment No. 4
Replace the administration of GSK2269557 via the DISKUS™ device (1000 µg) by a comparable dose administered via the ELLIPTA™ device (700 µg). GSK2269557 is no longer manufactured for use with the DISKUS device which will be replaced with ELLIPTA Device. To increase the number of patients to be recruited to obtain sufficient completers. Minor updates and clarifications.		

SPONSOR SIGNATORY

PPD

22.3.17.

Tony Cahn
Head of Respiratory Discovery, Respiratory R&D,
Stevenage.

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

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Primary Medical Monitor	PPD				Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
Secondary Medical Monitor					Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
SAE contact information	Medical monitor as above				

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980 Great West Road
Brentford
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UK**Structure and Content of a Clinical Study Protocol Amendment**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 201928

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201928

Rationale

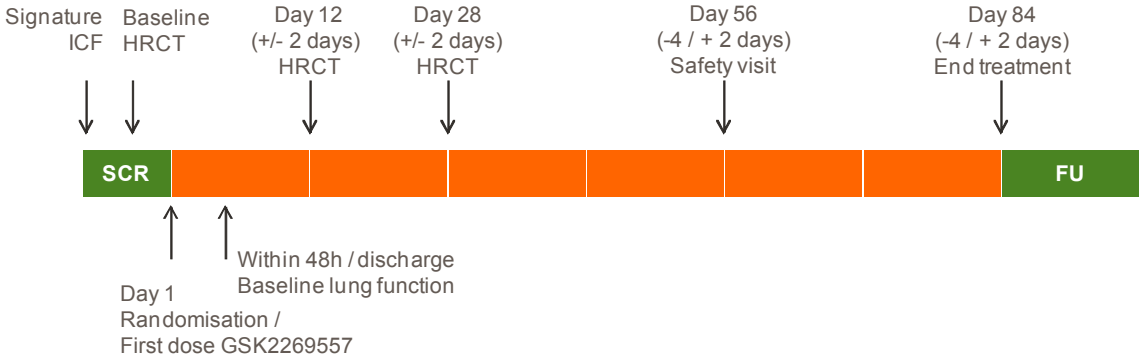
Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Haematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD.	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.	• PEF • Reliever usage • $FEV_{1\ and}$ FVC at clinic prior to sputum induction
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.

Objectives	Endpoints
exacerbation of COPD, compared to placebo.	
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment

Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual Chronic Obstructive Pulmonary Disease (COPD) medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The High-Resolution Computed Tomography (HRCT) scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (± 2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table. Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7-14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

Type and Number of Subjects

Approximately 45 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

Analysis

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

2. INTRODUCTION

GSK2269557 is a potent and highly selective inhaled Phosphoinositide 3-Kinase Delta (PI3Kδ) inhibitor being developed as an anti-inflammatory and anti-infective agent for the treatment of inflammatory airways diseases.

2.1. Study Rationale

The purpose of this study is to evaluate specific alterations in immune cell mechanisms related to neutrophil function as detected by PI3Kδ-dependent changes in mRNA extracted from induced sputum in patients experiencing an exacerbation of COPD. In addition this study will also further evaluate the plasma PK and assess the safety of GSK2269557 administered to patients diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD). The efficacy of treatment with GSK2269557 will also be measured using functional respiratory imaging (FRI) and spirometry.

This study will also explore the pharmacodynamic effects of once daily repeat doses of inhaled GSK2269557 on cytokines, mediators and microbiome in induced sputum samples. These will be obtained from subjects at entry, during their exacerbation, and at additional time points over the 12 week treatment period. To understand patient efficacy, at entry, Day 12 and Day 28 the sputum biomarker data will be correlated with computed tomography (CT).

2.2. Brief Background

PI3Kδ is a member of the Class IA family of phosphoinositides 3-kinases (PI3Ks) that convert the membrane phospholipid phosphatidylinositol 4,5-biphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is a second messenger in many cellular processes including cell growth, differentiation and migration. PI3Kδ has specific roles in mediating antigen receptor and cytokine signalling in T-cells, mast cells and B-cells [Okkenhaug, 2007] and roles in neutrophil chemotaxis and activation [Sadhu, 2003]. A PI3Kδ inhibitor has the potential to inhibit major cell types responsible for the inflammation associated with both COPD and asthma.

In COPD, tobacco smoke or other irritants activate epithelial cells and macrophages to release inflammatory mediators such as chemokines that attract neutrophils and T cells to the lungs. PI3Kδ is thought to play a role in a number of epithelial responses relevant for the development of COPD. Therefore a PI3Kδ inhibitor may be able to suppress a number of these processes [Kim, 2010]. A greater proportion of macrophages appear to be alternatively activated in COPD and their ability to phagocytose infective pathogens is reduced as a result of this alternative activation. PI3Kδ is one of the mediators involved in determining this alternative phenotype in macrophages and therefore it is proposed that inhibition of PI3Kδ might rebalance macrophage activation towards a classic phagocytic phenotype [Weisser, 2011] facilitating clearance of bacteria, a major cause of exacerbation in COPD. The neutrophil and T cell are the two major inflammatory cell types involved in the pathogenesis of COPD and both are targeted by PI3Kδ inhibitors.

GSK2269557 has demonstrated the ability to protect against and control bacterial infections in preclinical rodent models. This is coupled with recent observations that PI3Kδ inhibition leads to a correction in vitro of aberrant neutrophil chemotaxis directionality in the blood of COPD patients. Furthermore, a human point mutation which results in a constitutively activated version of PI3Kδ has recently been characterised where the majority of affected patients have recurrent lung infections with the same bacterial species which are seen in COPD patients and are known to drive exacerbations. Collectively these data suggest that repeat dosing with GSK2269557 could potentially reduce the impact of an acute exacerbation, or prevent the onset of a secondary bacterial exacerbation or recurrent exacerbation.

Proinflammatory cytokines were reduced by GSK2269557, both in preclinical rodent bacterial models, and COPD patient samples treated in vitro and in the study setting (PII115119).

GSK2269557 has been administered as single and repeat doses to healthy subjects as nebulized solution in the FTIH study PII115117 up to a dose of 6400 µg per day for 7 days. GSK2269557 has also been administered as single and repeat doses to healthy smokers as a dry powder formulation in study PII116617 up to a dose of 3000 µg as single dose and 2000 µg per day for 14 days. GSK2269557 has been well tolerated across the range of doses used. There is also an ongoing study (Study PII115119, non-reported) where a total daily dose of up to 2000 µg of GSK2269557 is being administered to stable COPD patients via a dry powder inhaler for 14 days in a two part study. Part A of this study has completed and Part B will characterise the steady-state (exposure) dose response following repeat inhaled doses of up to 2000µg for the same treatment duration. There is also a completed larger clinical study PII116678 which is almost identical in design to 201928 using 1000 µg of GSK2269557 per day administered via a Diskus dry powder inhaler to patients diagnosed with an acute exacerbation of COPD. For simplicity study PII116678 did not capture induced sputum hence cannot analyse any changes in mRNA. The primary objective of the current study is to capture induced sputum to enable the mRNA analysis on a smaller cohort.

GSK2269557 has also now been administered in Study 201544 using the formulation now proposed in this study up to daily doses of 200 µg GSK2269557 via the ELLIPTA™ DPI for up to 10 days. No safety issues were identified with this new formulation.

More information about the non-clinical and clinical studies is available in the GSK2269557 Investigator's Brochure (IB) GlaxoSmithKline Document Number 2012N141231_06.

2.2.1. Use of mRNA transcriptomics by Affymetrix

Analysis of changes in mRNA can be used to demonstrate alterations in biochemical pathways at the gene transcription level. This can be used to better understand the consequences of drug intervention on disease pathophysiology, and ultimately predict alterations which could translate to a positive clinical benefit for patients. Messenger RNA can be extracted from a variety of biological samples (including induced sputum and blood) taken from patients before and after drug dosing to show the impact a drug is having.

The advantage of using Affymetrix is the broad (~50k) gene set covered using this technology enabling great depth in exploring the biological consequences of drug intervention. This technology has been used in previous preclinical and clinical studies using GSK2269557 generating a fingerprint of PI3Kδ inhibition in disease. Importantly these approaches allow areas of complex PI3Kδ-dependent immune cell mechanisms and pathophysiology, specifically related to neutrophil function to be explored which are not easily quantified using other techniques.

2.2.2. Use of HRCT Endpoints to characterise Lung Function

High-resolution computed tomography (HRCT) scans provide a highly detailed insight into the structure and architecture of the respiratory system. A clear distinction can be made between the lung parenchyma, the intraluminal air and alveolar spaces up to the level of the smaller airways with a diameter of 1-2mm. To model dynamic information, low dose HRCT scans can be taken at two lung volumes: after deep inhalation (total lung capacity or TLC) and after normal expiration (functional residual capacity or FRC). The patient's breathing is monitored in real time during the scans to ensure the correct lung levels are scanned. Due to the natural contrast between the intraluminal air and the surrounding tissue, it is possible to attain a significant reduction in radiation dose (1-2 mSv per scan) compared to standard CT protocols (>4 mSv per scan) by reducing the tube current and the voltage. Depending on the patient's weight, a 6- to 10-fold reduction can be obtained per scan without losing image quality. As a comparison, in the USA, the average annual background radiation exposure is 6.2 mSv and a transatlantic flight results in 0.07 mSv exposure.

The high resolution images allow for a three dimensional reconstruction of the airway tree and vasculature by applying segmentation principles. These three dimensional models can be used to measure airway dimensions as well as potentially allowing the phenotyping of patients by disease severity. The three dimensional computer reconstructions can be used for fluid dynamic modelling. This method is used to simulate flow through these airway models and determine the typical flow characteristics such as local pressure drops, velocities and resistance. It can also be used to predict particle deposition in the airways of these patients when using inhaled drug products.

This method consisting of 2 low dose HRCT scans at several time points has previously been used successfully in clinical trials involving COPD patients [De Backer, 2011; De Backer, 2012; De Backer, 2014; Goldin, 1999].

3. OBJECTIVE(S) AND ENDPOINT(S)

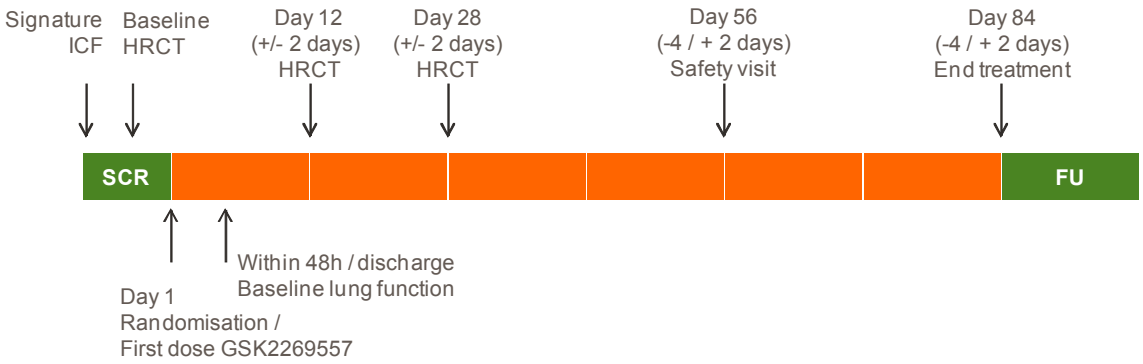
Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Hematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD, compared to placebo	• PEF, Reliever usage. • FEV_1 and FVC at clinic prior to sputum induction.
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.

Objectives	Endpoints
administered to subjects with acute exacerbation of COPD, compared to placebo.	
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment.

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual COPD medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



4.2. Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The HRCT scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (±2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table (Section 7.1). Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7 to 14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

4.3. Type and Number of Subjects

Approximately 45 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

4.4. Design Justification

This study will include a placebo control to allow for a valid evaluation of the pharmacodynamic endpoints and adverse events attributable to treatment versus those independent of treatment. Subjects will also receive standard of care for their exacerbation and throughout the study.

4.5. Dose Justification

The dose chosen for this study is 700 µg of GSK2269557 per day administered via a dry powder ELLIPTA inhaler for a duration of 84 days (– 4 / + 2 days) and is equivalent to the dose of 1000 µg administered via DISKUS in terms of the dose deposited and systemic exposure. This dose has been selected based on previous safety and tolerability data in man, obtained in healthy subjects, healthy smokers and COPD patients including patients suffering COPD exacerbations. Also dose selection is based on a healthy subjects study using the ELLIPTA™ DPI. It will be assumed for exposure predictions, unless otherwise stated, that patients suffering exacerbations will have a similar lung deposition, distribution and plasma exposure to that of the healthy volunteers. However it is accepted that these types of subjects may have reduced airway function and hence potentially reduced deposition. This can be appropriately defined in this study based on the actual plasma exposures achieved.

For DISKUS, twice this dose level (2000 µg) using the same formulation has previously been given once daily to healthy male smokers for 14 days (study PII116617). There is also an ongoing study where a total daily dose of 1000 µg of GSK2269557 is administered to stable COPD subjects via a dry powder inhaler for 14 days (study PII115119) which at the time of writing of this protocol had successfully dosed 21 subjects on active treatment and collected pharmacokinetics (PK) samples for analysis out to 14 days.

The target effect compartment for PI3Kδ inhibition is the intracellular compartment of the immune cells resident in the lung tissue and lumen. GSK2269557 has a high potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL) which translates into an IC_{50} in a more complex system (PHA stimulated lung tissue) of approximately 120 ng/mL (or 2.5 ng/mL free unbound drug). Based on the measured steady-state cellular concentration of GSK2269557 collected at trough (24 h) from the lungs of healthy smokers at 2000 µg DPI (450 ng/mL) in the clinical study it is expected that at 1000 µg (225 ng/mL), concentrations will be sufficient and PI3Kδ inhibition maintained in the lung at ≥ 90% inhibition for 24 h.

Target PI3Kδ inhibition is based on a wide range of pharmacology experiments. Details of these as well as the pharmacokinetics and safety data can be found in the IB, [GlaxoSmithKline Document Number: 2012N141231_06].

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2269557 can be found in the IB [GlaxoSmithKline Document Number

2012N141231_06]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm	A general risk with Inhaled treatment	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on screening, Day 12 and Day 28 visits) at are required throughout the study for the functional imaging protocol	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be approximately 12mSv. Final radiation dose will be dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk). The outcomes of this study will provide information which would produce advances in knowledge, leading to a potential health benefit in the future for patients in this target

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		population. The CT may also provide information for the patients general clinical management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation.	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the opinion of the Investigator, it is considered safe to do so.

4.6.2. Benefit Assessment

The outcomes of this study will provide information which will produce advances in knowledge of the pathophysiology of COPD exacerbations, leading to a potential health benefit in the future for patients in this target population. The CT scan may also provide information for the patient's general clinical management.

4.6.3. Overall Benefit:Risk Conclusion

The overall benefit:risk is considered to be positive. There is an opportunity to determine if there may be a new drug developable for the treatment of acute exacerbations of COPD which has not seen any new treatments recently. The scientific value in obtaining functional CT information on the anatomy and pathophysiology of COPD exacerbations

and how the lung responds to therapy will be extremely valuable to the wider clinical community and justifies the limited radiation exposure (maximum 12 mSv in total) from the CT scan procedures. The CT will also be useful to provide clinical information about the patient for the patient's physician and contribute to clinical management.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number: 2012N141231_06]

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

[1] AGE
• Between 40 and 80 years of age inclusive, at the time of signing the informed consent.
[2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
• The subject has a confirmed and established diagnosis of COPD, as defined by the GOLD guidelines for at least 6 months prior to entry. • The subject is able to produce >100 mg of sputum at screening for processing, (ie, total weight of sputum plugs.). • The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted documented in the last 5 years. • Disease severity: Acute exacerbation of COPD requiring an escalation in therapy to include both corticosteroid and antibiotics. Acute exacerbation to be confirmed by an experienced physician and represent a recent change in at least two major and one minor symptoms, one major and two minor symptoms, or all 3 major symptoms. 1. Major symptoms: • Subjective increase in dyspnea • Increase in sputum volume • Change in sputum colour 2. Minor symptoms:

- Cough
- Wheeze
- Sore throat

- The subject is a smoker or an ex-smoker with a smoking history of at least 10 pack years (pack years = (cigarettes per day smoked/20 x number of years smoked)).

[3] WEIGHT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 16 – 35 kg/m^2 (inclusive).

[4] SEX

- Male
- Female subject : is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

1. Non-reproductive potential defined as:

Pre-menopausal females with one of the following:

Documented tubal ligation

Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion

Hysterectomy

Documented Bilateral Oophorectomy

Postmenopausal defined as 12 months of spontaneous amenorrhea. Females whose menopausal status is in doubt will be required to use, or have been using, one of the highly effective contraception methods as specified below from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

2. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets GSK standard criteria

including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]

3. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
4. Injectable progestogen [Hatcher, 2007a]
5. Contraceptive vaginal ring [Hatcher, 2007a]
6. Percutaneous contraceptive patches [Hatcher, 2007a]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
8. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Specific inclusion criteria for Male subjects with female partners of reproductive potential is outlined below:

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until after the completion of the follow up visit.

3. Vasectomy with documentation of azoospermia.
4. Male condom plus partner use of one of the contraceptive options below:

Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label

Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]

Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a]

Contraceptive vaginal ring [Hatcher, 2007a]

Percutaneous contraceptive patches [Hatcher, 2007a]

5. These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

[5] INFORMED CONSENT
• Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

• To avoid recruitment of subjects with a severe COPD exacerbation, the presence of any one of the following severity criteria will render the subject ineligible for inclusion in the study:
  • Need for invasive mechanical ventilation (short term (< 48h) NIV or CPAP is acceptable)
  • Haemodynamic instability or clinically significant heart failure
  • Confusion
  • Clinically significant pneumonia, identified by chest X-ray at screening, and as judged by the Investigator.
• Subjects who have current medical conditions or diseases that are not well controlled and, which as judged by the Investigator, may affect subject safety or influence the outcome of the study. (Note: Patients with adequately treated and well controlled concurrent medical conditions (e.g. hypertension or NIDDM) are permitted to be entered into the study).
• Subject has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the subject or affect the interpretation of the results.
• ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
• A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the exclusion criteria, outside of the reference range for the population being studied may be included if the Investigator [in consultation with the GSK Medical Monitor if required] documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
• Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
• ECG indicative of an acute cardiac event (e.g. Myocardial Infarction) or demonstrating a clinically significant arrhythmia requiring treatment.
• QTcF > 450 msec or QTcF > 480 msec in subjects with Bundle Branch Block, based on single QTcF value.
• Subjects who have undergone lung volume reduction surgery.

[2] CONCOMITANT MEDICATIONS
• Subject is currently on chronic treatment with macrolides or long term antibiotics. • Subject is being treated with long term oxygen therapy - LTOT (> 15 hours/day). • The subject has been on chronic treatment with anti-Tumour Necrosis Factor (anti-TNF), or any other immunosuppressive therapy (except corticosteroid) within 60 days prior to dosing.

[3] RELEVANT HABITS
• History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >28 units for males or >21 units for 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.

[4] CONTRAINDICATIONS
• History of sensitivity to any of the study medications, or components thereof (such as lactose) or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

[5] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
• A known (historical) positive test for HIV antibody. • Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. NOTE: Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor. • Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. • The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). • Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal

set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria Protocol Deviations, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn should complete all the assessments planned, if possible. Subjects who are withdrawn **on a study clinic visit** after randomization should complete all the safety related assessment for that visit which includes at minimum, vital sign, lab assessments (if deem necessary by the PI), AE/SAEs, concomitant medication(s) and ECG. A Follow up Visit should be scheduled 7-14 days post last dose.

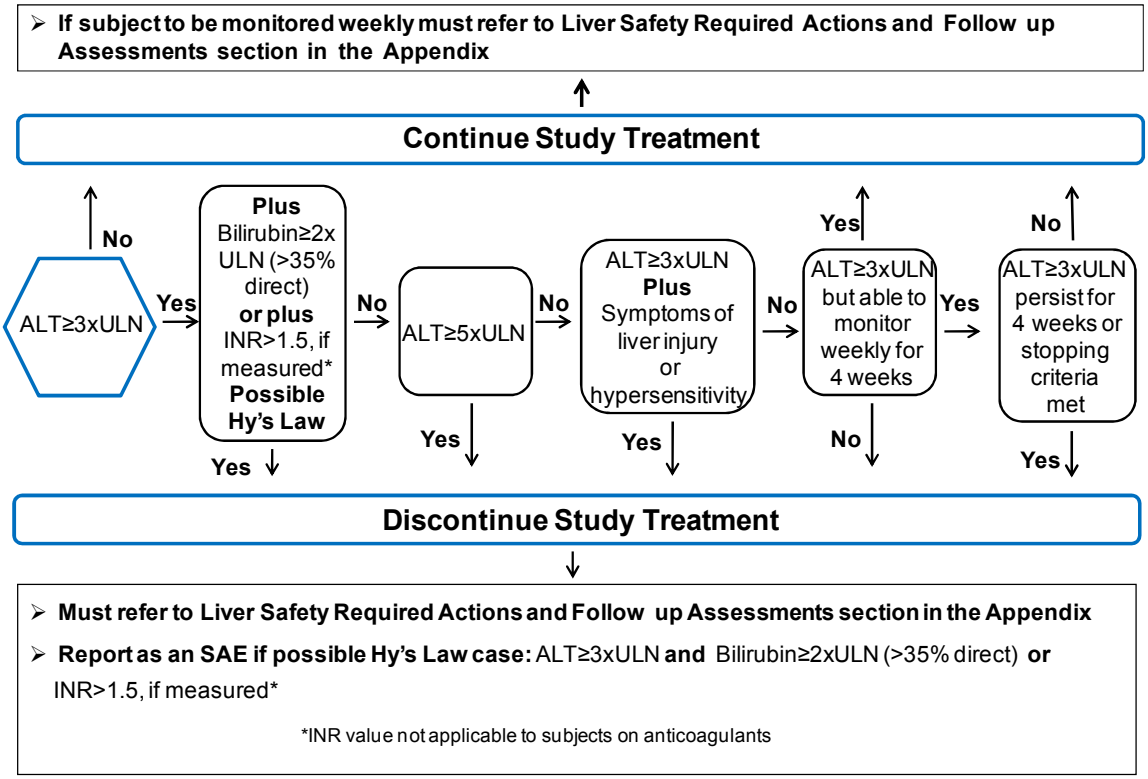
Subjects who are withdrawn **in between study clinic visits** should complete the unscheduled visit and complete all the safety related assessment at minimum which includes, vital sign, lab assessments (if deem necessary by the PI), AEs/SAEs, concomitant medication(s) and ECG. A Follow up Visit should be scheduled 7-14 post last dose.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.1.1. Study Treatment Restart or Re-challenge

Study treatment restart or re-challenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.2. QTc Stopping Criteria

- QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. For example, if an ECG (Electrocardiogram) demonstrates a prolonged QTcF interval, obtain two more ECGs and use the averaged QTcF values of the three ECGs to determine whether the patient should be discontinued from the study.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

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

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

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

5.4.3. Other Stopping Safety Criteria

For an individual study participant, stopping criteria include, but are not limited to:

Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests, spirometry assessments, etc), as judged by the Principal Investigator in consultation with the Medical Monitor if necessary.

Treatment failure or recurrent exacerbation does **not** mandate withdrawal from the study, unless there is a safety concern as judged by the Investigator, in consultation with the Medical Monitor if necessary.

Subjects should be withdrawn from the study if confusion, acute respiratory acidosis (pH < 7.30), or need for invasive mechanical ventilation occurs.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Study Treatment Name:	GSK2269557 ELLIPTA™ DPI (100 µg)	GSK2269557 ELLIPTA™ DPI (500 µg)	Placebo ELLIPTA™ DPI
Formulation description:	GSK2269557 blended with lactose and magnesium stearate	GSK2269557 blended with lactose and magnesium stearate	Lactose
Dosage formulation:	DPI	DPI	DPI
Unit dose strength(s)/Dosage level(s):	100 µg per blister	500 µg per blister	NA
Route of Administration:	Inhaled	Inhaled	Inhaled
Dosing instructions:	Inhale as directed	Inhale as directed	Inhale as directed
Physical description:	Dry white powder	Dry white powder	Dry white powder
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	Study Treatment will be labeled as required per country requirement.	Study Treatment will be labeled as required per country requirement.	Study Treatment will be labeled as required per country requirement.
Manufacturer	GSK	GSK	GSK

6.2. Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Central based randomisation will be used.

Subjects will be randomised to treatments A, B, C or D where:

A = Placebo

B = GSK2269557 1000 µg

C = Placebo via Ellipta

D = GSK2269557 700 µg via Ellipta

A web based interactive response system will be used to assign subjects to treatment.

6.3. Planned Dose Adjustments

If adverse events, unrelated to COPD exacerbation, which are of moderate or severe intensity and are consistent across subjects in the group, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK2269557, are observed in more than 30% of the subjects then the study will be halted and no further subject will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the Ethics Committees will then take place prior to any resumption of dosing. If the above is observed consideration may be given to reducing the dose of GSK2269557 to 500 µg O.D.

6.4. Subject Specific Dose Adjustment Criteria

There are no subject specific dose adjustment criteria.

6.5. Blinding

This will be a double blind study and the following will apply.

- The investigator or treating physician may un-blind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** un-blinding the subject's treatment assignment.
- If GSK personnel are not contacted before the un-blinding, the investigator must notify GSK as soon as possible after un-blinding.
- The date and reason for the un-blinding must be fully documented in the Case Report Form (CRF)
- A subject will be withdrawn if the subject's treatment code is un-blinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the un-blinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may un-blind the treatment assignment for any subject with a Serious Adverse Event (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 subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects 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 labelled 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 (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for 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.

6.7. Compliance with Study Treatment Administration

When subjects 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 subjects will be asked to complete a diary when dose administration takes place at home. The date, time and number of inhalations will be recorded. The compliance will be checked by the site staff at each planned visit.

A record of the number of ELLIPTA™ inhalers dispensed to each subject and the number of actuation administered, read from the dose counter for each ELLIPTA™ inhaler, must be maintained and reconciled with study treatment and compliance records.

Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK2269557 >2000 µg for DISKUS and >1400 µg for ELLIPTA within a 22 hour time period will be considered an overdose.

GSK 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 subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2269557 can no longer be detected systemically (at least 14 days for GSK2269557)
3) obtain a plasma sample for pharmacokinetic (PK) analysis within 7 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 subject.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Any clinical abnormalities identified during the conduct of the study will be locally managed by the Investigator.

6.10. Lifestyle and/or Dietary Restrictions

- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.
- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit, and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study and in such case, subjects should be advise to discontinue their own ventolin and use the study ventolin and aerochamber provided for the duration of the study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

6.11.2. Prohibited Medications and Non-Drug Therapies

Regular or chronic treatment with medications that are considered strong inhibitors of CYP3A4 or CYP2D6 are not permitted. This includes anti-epileptic treatments, macrolide antibiotics, oral antifungal treatments (single doses and courses up to 7 days are allowed) and anti-tuberculous therapy. These medications must all have been stopped at least 14 days prior to first dose.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table (Screening and Follow Up Visits)

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Informed consent	X		
Demography	X		
Inclusion and exclusion criteria	X		
Full physical exam, including height and weight	X		
Brief physical examination, including weight		X	
Chest X-Ray	X		To be done before baseline HRCT to exclude significant pneumonia and other incidental serious underlying pathology.
Medical history (includes substance usage and Family history of premature CV disease)	X		Substances: Drugs, Alcohol, tobacco via history. No drug, alcohol screening is required.
Past and current medical conditions (including cardiovascular medical history and therapy history)	X		
Laboratory assessments (include Hematology and biochemistry)[1]	X	X	Historical values analysed by local lab to be used for eligibility assessment. Another sample must be collected and sent to central lab as soon as informed consent is obtained.
Hep B and Hep C screen[2]	X		
Urine pregnancy test (only WCBP)	X		Before conducting the HRCT. Done locally at the site.
12-lead ECG	X	X	Single assessment
Vital signs	X	X	Single assessment
HRCT (at TLC and FRC)	X		Within 48 h of diagnosis, if subject otherwise eligible. Includes electronic monitoring of breathing (if applicable). Baseline HRCT will be reviewed by the local site's radiologist to identify any significant occurring underlying medical conditions that require further clinical management or monitoring.
Induced Sputum[3]	X[4]		To include sputum culture pre-first dose. Culture to be done by the local site laboratory.
Blood sample for mRNA Analysis	X[4]		Collected at any time on specified days
AE/SAE collection and review		X	

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Concomitant medication review	X	X	

1. Due to the short screening window, central laboratory analysis results will not be available on time. Therefore the local laboratory results should be used for eligibility assessment (to exclude severe subjects and underlying medical conditions). If local laboratory results are already available from diagnosis of current exacerbation, there is no need to take another sample for local analysis. A sample for central laboratory analysis should also be obtained. See Section 7.8.6 for further details.
2. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required. Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor.

3. Induced sputum collection may be attempted on several occasions if an adequate sample is not produced at the first attempt.
4. To be collected at any time point before randomisation.

7.2. Time and Events Table (Treatment Period)

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
ELLIPTA™ Inhaler Training	X						Training conducted by reviewing the Patient Information Leaflet with the subject (no device will be used). Additional training may be conducted at the discretion of the investigator
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	
Diary Card dispense and review at clinic	X		X	X	X	X	Refer to SRM for details.

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========					==========→	Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

1. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
2. Assessments do not need to be completed if screening assessments conducted within 48 hours
3. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
4. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

7.3. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

If they are being utilised in the study, Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

7.4. Biomarker(s)/Pharmacodynamic Markers

7.4.1. Pharmacodynamic Biomarkers in Sputum

- Collect sputum induction samples at the time-points shown in the time and events table (Section 7.1).
- The sputum induction collection process will follow local standard procedures and guidelines outlined in the SRM.
- The collection of induced sputum may be attempted on several occasions if an adequate sample is not produced at the first attempt.
- Further information on collection, processing, storage and shipping procedures are provided in the SRM.

7.4.2. mRNA in blood

- Collect 2.5 mL of blood into a PAXgene mRNA tube.

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

7.5. Patient diary

The subjects will be provided with a diary to record the following data when at home:

- Time and date of each dose administration and number of inhalations.
- Adverse Events and concomitant medications taken (including daily rescue medication – if used and how many times used).

- PEF from a handheld device. The best/highest result is recorded.

Changes in Health and details of any concomitant medications as well as PEF assessment details will be collected in the paper diaries and later transcribed into the CRF.

7.6. Genetics

Information regarding genetic research is included in Appendix 3.

7.7. Efficacy

7.7.1. Functional Respiratory Imaging

- A CT scan with a low radiation protocol at FRC and TLC will be conducted as listed in the Time and Events Table (Section 7.1). The same scanner should be used for baseline and post-treatment scans for an individual subject.
- A urine pregnancy test should be performed before the CT scan in female subjects of childbearing potential.
- Further information is provided in the SRM.

7.7.2. FEV_1 and FVC

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. These will be recorded as absolute values. The best/highest result is recorded.

- Further details are provided in the SRM.

7.7.3. Peak Expiratory Flow PEF

- PEF measurements will be taken (in triplicate) daily in the morning before dose administration, as soon as it is safe for the subject to do so. The best/highest result is recorded.
- Subjects will be provided with a handheld device.
- Further details are provided in the SRM.

7.8. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.8.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.8.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.8.1.3), at the time-points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.8.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.8.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

7.8.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

7.8.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless they meet the definition of an SAE as defined in Appendix 4 Exacerbations that meet the definition of an SAE will be recorded on the appropriate eCRF section and should be reported to GSK.

Medications used to treat a COPD exacerbation will be recorded in the exacerbation eCRF

7.8.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.8.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until the follow-up visit
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.8.3. Physical Exams

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

7.8.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.
- Three readings of blood pressure and pulse rate will be taken
- First reading should be rejected
- Second and third readings should be averaged to give the measurement to be recorded in the CRF.

7.8.5. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at screening and at each other timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

7.8.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Historical values (if the assessment was conducted as part of the standard of care) for blood gases, blood culture and sputum culture may also be collected if available.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Table 1 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential:</u></td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose (non fasted)</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
<tr><td>CRP</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>• Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)</td></tr>
</table>

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 5.4.1 and Appendix 2
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Hematology and clinical chemistry at screening for excluding subjects with severe disease and uncontrolled medical conditions. The results of each test must be entered into the CRF.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Hematology, clinical chemistry and additional parameters to be tested are listed in Table 1.

7.9. Pharmacokinetics

7.9.1. Blood Sample Collection

A 2 mL blood samples for pharmacokinetic (PK) analysis of GSK2269557 will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.9.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK2269557 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for GSK2269557 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK/Scinovo, GlaxoSmithKline protocol.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

This study is designed to establish the PI3Kδ-dependent alterations in immune cell mechanisms related to neutrophil function as detected by changes in mRNA transcriptomics in samples of induced sputum from patients admitted with an exacerbation of COPD. The primary comparison will be between subjects treated with GSK2269557 in addition to standard of care, and subjects treated with placebo in addition to standard of care. In addition, treatment comparisons between subjects at baseline and subsequent time points will also be produced. By first intent, the data from the different devices will be pooled and may also be investigated separately, full details will be specified in the RAP prior to unblinding.

9.1. Sample Size Considerations

The sample size for this study has been based on feasibility. The sample size of 30 subjects completing the trial, with approximately 15 of which will receive GSK2269557 and 15 will receive placebo, is expected to be sufficient to provide a meaningful estimate of the mRNA alterations within the lungs.

Previous studies with similar sample size populations have yielded significant fold-changes (fold-change>1.5 and $p<0.05$) in immune cell mechanisms using the changes in mRNA transcriptomics.

Study Name	Sample	Study Design	Number of Subjects	Number of Differential probesets FC = >= 1.5, Pval <= 0.05	Notes
PII115117 FTIH Healthy Smoker nebulised GSK2269557	Sputum	Sputum N=12 3-way x-over placebo 400ug, 6400ug	12 (9 with all data points)	57 probesets change with both doses = 44 Genes	Gene changes relate predominantly to a down regulation of infection and inflammation responses. Link to Haemophilus influenzae and Moraxella catarrhalis infection biology – Identified prior to knowledge of Activated PI3Kδ Syndrome phenotype
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Sputum	Ex vivo Sputum incubated with GSK2269557 sampled at 6hrs (Sputum producers)	15 Subjects	490 probesets change vs vehicle control = 295 genes (of which 43 are dysregulated in COPD disease vs Healthy comparison)	43 genes altered in COPD and positively modulated by PI3Kδi GSK2269557. Biological themes in signature: Pro-cell movement/migration and cell viability, anti-apoptotic. Additionally link to B/T cell function. Signature supports GSK2269557 correction of neutrophil migration
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at 6hrs (Sputum	15 Subjects	19 probesets change vs vehicle control = 15 genes	Infection and inflammation associated genes
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at	15 Subjects	30 probesets change vs vehicle control = 25 genes	Infection and inflammation associated genes

9.1.1. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed in this study.

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Screened	• All subjects who were screened.	• Study Population
All subject	• All randomised subjects who receive at least one dose of the study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Pharmacodynamics • Safety • Efficacy
Pharmacokinetic	• Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.	• PK

9.2.2. Interim Analysis

No interim analyses will be performed.

9.3. Key Elements of Analysis Plan

9.3.1. Primary Analyses

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

Further details around the analysis of the mRNA data will be provided in the RAP.

9.3.2. Secondary Analyses

All secondary analyses will be described in full prior to unblinding in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)

- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all

relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
ECG	Electrocardiogram
DPI	Dry Powder Inhaler
FEV1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
GCP	ICH Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
PEF	Peak Expiratory Flow
PI3Kδ	Phosphoinositide 3-Kinase Delta
PK	Pharmacokinetic
QTcF	QT interval corrected using the Fridericia's formula
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SRM	Study Reference Manual
TLC	Total Lung Capacity
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DISKUS
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **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 subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (refer to Appendix 2). • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained 7 days after last dose[5] • 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

treatment and may continue subject in the study for any protocol specified follow up assessments	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form
MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • 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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, 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 subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. PK sample may not be required for subjects 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 blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.3. Appendix 3: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- COPD susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to

the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where 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.

12.4.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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 disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are 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

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject'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 instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject 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 the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication

Pregnancy information on female partner of male study subjects

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks 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: Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7: Protocol Amendment Changes

Protocol Amendment #1 Changes

The amendment was created to remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria (European Community of Coal and Steel and European Respiratory Society Global Lung Function Initiative reference equations (Quanjer 2012) in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. As a result it may not be valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.

List of specific changes:

Page 22, Inclusion Criteria (#2 – Type of Subject and Diagnosis Including Disease Severity) - Third Bullet.

PREVIOUS TEXT

- The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted. Predictions should be according to the European Community of Coal and Steel (ECCS) equations OR the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012] and documented in the last 5 years.

REVISED TEXT

- The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted documented in the last 5 years.

Page 40, Section 7.7.2 (FEV_1 and FVC)

PREVIOUS TEXT

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. Predicted values will be based upon the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012].

REVISED TEXT

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. These will be recorded as absolute values. The best/highest result is recorded.

Page 54 – References

PREVIOUS TEXT

De Backer J, Vos W, Vinchurkar S, Van Holsbeke C, Poli, G, Claes R et al. The Effect of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Fundtional Respiratory Imaging. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:1-12.

De Backer LA, Vos WG, Salgado R, De Backer JW, Devoldr A, Verhulst SL et al. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD. *International Journal of COPD.* 2011;6:637-646.

De Backer Lieve A, Vos Wim, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. *Eur Respir J.* 2012;40:298-305.

GlaxoSmithKline Document Number 2012N141231_06: GSK2269557 Investigator's Brochure. Report Date 12-FEB-2015.

Goldin J, Tashkin D, Kleerup E, Greaser MS, Haywood U, Sayre J et al. Comparative effects of hydrofluoroalkane and chloroflurocarbon beclomethasone dipropionate inhalation on small airways: Assessment with functional helical thin-section computed tomography. *J Allergy Clin Immunol.* 1999;104 #6:S258-S267.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(a):24. Table 3-2.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(b): 28.

ICRP. 2007 Recommendation of the International Commission on Radiological Protection. *ICRP Publication 103.* 2007;37:2-4.

Kim SR, Lee KS, Park HS, et al. HIF -1 alpha inhibition ameliorates an allergic airway disease via VEGF suppression in bronchial epithelium. *Eur J Immunol.* 2010;40 (10):2858-69.

Okkenhaug K, Aki K, Vanhaesebroeck B. Antigen receptor signalling: A distincive role for the p110 isoform of PI3K. *Trends in Immunuology.* 2007;28:80-7.

Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *European Respiratory Journal.* 2012;40(6):1324-1343.

Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI13K delta in neutrophil inflammatory responses. *Biochem Biophys Res Commun.* 2003 Sep 5;308 (4):764-9.

Weisser SB, McLarren KW, Voglmaier B, et al. Alternative activation of macrophages by IL-4 requires SHIP degradation. *Eur J Immunol.* 2011;41(6):1742-53.

REVISED TEXT

De Backer J, Vos W, Vinchurkar S, Van Holsbeke C, Poli, G, Claes R et al. The Effect of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Fundtional Respiratory Imaging. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:1-12.

De Backer LA, Vos WG, Salgado R, De Backer JW, Devoldr A, Verhulst SL et al. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD. *International Journal of COPD.* 2011;6:637-646.

De Backer Lieve A, Vos Wim, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. *Eur Respir J.* 2012;40:298-305.

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Goldin J, Tashkin D, Kleerup E, Greaser MS, Haywood U, Sayre J et al. Comparative effects of hydrofluoroalkane and chloroflurocarbon beclomethasone dipropionate inhalation on small airways: Assessment with functional helical thin-section computed tomography. *J Allergy Clin Immunol.* 1999;104 #6:S258-S267.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(a):24. Table 3-2.

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ICRP. 2007 Recommendation of the International Commission on Radiological Protection. *ICRP Publication 103.* 2007;37:2-4.

Kim SR, Lee KS, Park HS, et al. HIF -1 alpha inhibition ameliorates an allergic airway disease via VEGF suppression in bronchial epithelium. *Eur J Immunol.* 2010;40 (10):2858-69.

Okkenhaug K, Aki K, Vanhaesebroeck B. Antigen receptor signalling: A distincive role for the p110 isoform of PI3K. *Trends in Immunuology.* 2007;28:80-7.

Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI13K delta in neutrophil inflammatory responses. *Biochem Biophys Res Commun.* 2003 Sep 5;308 (4):764-9.

Weisser SB, McLarren KW, Voglmaier B, et al. Alternative activation of macrophages by IL-4 requires SHIP degradation. *Eur J Immunol.* 2011;41(6):1742-53.

Protocol Amendment #2 Changes

This amendment was created to widen the Body Mass Index (BMI) range at the screening visit as the propose range from 16 – 35 kg/m^2 would be appropriate for the COPD subject population.

List of specific changes:

Page 22, Inclusion Criteria (#3 – Weight).

PREVIOUS TEXT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 18 – 32 kg/m^2 (inclusive).

REVISED TEXT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 16 – 35 kg/m^2 (inclusive).

Protocol Amendment #3 Changes

This amendment was created to remove the photo toxicity from the protocol as a result of the updated Investigator Brochure, Version 7.0, August16, 2016. It also contains minor administrative and clarification changes.

List of specific changes:

PREVIOUS TEXT

Section 4.6.1 (Table) – Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm	A general risk with Inhaled treatment	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Potential photosensitivity	In the absorption spectrum for GSK2269557 there are peaks at the boundary of the ultraviolet (UV) light [UVA/UVB] region with a lambda max at 320 nm (molar extinction coefficient 43800 L/Mol/cm), with smaller peaks at 305 nm and 332 nm.	Subjects will be advised to take UV protection measures (see Section 6.11).
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on screening, Day 12 and Day 28 visits) at are required	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be approximately 12mSv. Final radiation dose will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	throughout the study for the functional imaging protocol	dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk). The outcomes of this study will provide information which would produce advances in knowledge, leading to a potential health benefit in the future for patients in this target population. The CT may also provide information for the patients general clinical management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation.	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the opinion of the Investigator, it is considered safe to do so.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy

REVISED TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm	A general risk with Inhaled treatment	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on screening, Day 12 and Day 28 visits) at are required throughout the study for the functional imaging protocol	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be approximately 12mSv. Final radiation dose will be dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk). The outcomes of this study will provide information which would produce advances in

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		knowledge, leading to a potential health benefit in the future for patients in this target population. The CT may also provide information for the patients general clinical management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation.	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the opinion of the Investigator, it is considered safe to do so.

PREVIOUS TEXT

Apply to **ALL** sections with reference to IB, [GlaxoSmithKline Document Number: 2012N141231_**04**].

REVISED TEXT

Replace with:

IB, [GlaxoSmithKline Document Number: 2012N141231_**06**].

PREVIOUS TEXT

SECTION 5.4 – Withdrawal/Stopping Criteria

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn should complete the assessments planned for the follow up visit.

REVISED TEXT

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn should complete all the assessments planned, if possible. Subjects who are withdrawn **on a study clinic visit** after randomization should complete all the safety related assessment for that visit which includes at minimum, vital sign, lab assessments (if deem necessary by the PI), AE/SAEs, concomitant medication(s) and ECG. A Follow up Visit should be scheduled 7-14 days post last dose.

Subjects who are withdrawn **in between study clinic visits** should complete the unscheduled visit and complete all the safety related assessment at mininum which includes, vital sign, lab assessments (if deem necessary by the PI), AEs/SAEs, concomitant medication(s) and ECG. A Follow up Visit should be scheduled 7-14 post last dose.

PREVIOUS TEXT

SECTION 6.11 – Lifestyle and/or Dietary Restrictions

- Subjects must not sunbathe or use a tanning device (e.g. sunbed or solarium) whilst taking the study medication and until at least 2 weeks after their last dose. Subjects are to be advised that they should cover exposed areas of skin (e.g. use sun hat, long sleeves) and use a broad spectrum UVA/UVB sunscreen (SPF ≥30) on exposed areas of skin when outdoors.
- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.

- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

REVISED TEXT

- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.
- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

PREVIOUS TEXT

SECTION 6.12.1 – Permitted Medications and Non-Drug Therapies

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit, and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

REVISED TEXT

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit, and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study and in such case,subjects should be advise to discontinue their own ventolin and use the study ventolin and aerochamber provided for the duration of the study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

PREVIOUS TEXT

SECTION 7.2 – Time and Events Table (Treatment Period)

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

5. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
6. Assessments do not need to be completed if screening assessments conducted within 48 hours
7. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
8. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

REVISED TEXT

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	
Diary Card dispense and review at clinic	X		X	X	X	X	Refer to SRM for details.

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

9. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
10. Assessments do not need to be completed if screening assessments conducted within 48 hours
11. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
12. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

PREVIOUS TEXT

SECTION 11 – References

GlaxoSmithKline Document Number 2012N141231_04: GSK2269557 Investigator's Brochure. Report Date 12-FEB-2015.

REVISED TEXT

GlaxoSmithKline Document Number 2012N141231_06: GSK2269557 Investigator's Brochure. Report Date 16-AUG-2016.

Protocol Amendment #4 Changes

Replace the administration of GSK2269557 via the DISKUS™ device (1000 μg) by a comparable dose administered via the ELLIPTA™ device (700 μg). GSK2269557 is no longer manufactured for use with the DISKUS device which will be replaced with ELLIPTA Device. To increase the number of patients to be recruited to obtain sufficient completers. Minor updates and clarifications.

SECTION 1 – Type and Number of Subjects

PREVIOUS TEXT

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected numbers of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

REVISED TEXT

Approximately 45 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

SECTION 2.2 – Brief Background (5th Paragraph)

PREVIOUS TEXT

GSK2269557 has been administered as single and repeat doses to healthy subjects as nebulized solution in the FTIH study PII115117 up to a dose of 6400 μg per day for 7 days. GSK2269557 has also been administered as single and repeat doses to healthy smokers as a dry powder formulation in study PII116617 up to a dose of 3000 μg as single dose and 2000 μg per day for 14 days. GSK2269557 has been well tolerated across the range of doses used. There is also an ongoing study (Study PII115119, non-reported) where a total daily dose of up to 2000 μg of GSK2269557 is being administered to stable COPD patients via a dry powder inhaler for 14 days in a two part study. Part A of this study has completed and Part B will characterise the steady-state (exposure) dose response following repeat inhaled doses of up to 2000μg for the same treatment duration. There is also a completed larger clinical study PII116678 which is almost identical in design to 201928 using 1000 μg of GSK2269557 per day administered via a Diskus dry powder inhaler to patients diagnosed with an acute exacerbation of COPD. For simplicity study PII116678 does not capture induced sputum hence cannot analyse any changes in mRNA. The primary objective of the current study is to capture induced sputum to enable the mRNA analysis on a smaller cohort.

REVISED TEXT

GSK2269557 has been administered as single and repeat doses to healthy subjects as nebulized solution in the FTIH study PII115117 up to a dose of 6400 µg per day for 7 days. GSK2269557 has also been administered as single and repeat doses to healthy smokers as a dry powder formulation in study PII116617 up to a dose of 3000 µg as single dose and 2000 µg per day for 14 days. GSK2269557 has been well tolerated across the range of doses used. There is also an ongoing study (Study PII115119, non-reported) where a total daily dose of up to 2000 µg of GSK2269557 is being administered to stable COPD patients via a dry powder inhaler for 14 days in a two part study. Part A of this study has completed and Part B will characterise the steady-state (exposure) dose response following repeat inhaled doses of up to 2000µg for the same treatment duration. There is also a completed larger clinical study PII116678 which is almost identical in design to 201928 using 1000 µg of GSK2269557 per day administered via a Diskus dry powder inhaler to patients diagnosed with an acute exacerbation of COPD. For simplicity study PII116678 did not capture induced sputum hence cannot analyse any changes in mRNA. The primary objective of the current study is to capture induced sputum to enable the mRNA analysis on a smaller cohort.

GSK2269557 has also now been administered in Study 201544 using the formulation now proposed in this study up to daily doses of 200 µg GSK2269557 via the ELLIPTA™ DPI for up to 10 days. No safety issues were identified with this new formulation.

SECTION 4.3 – Type and Number of Subjects

PREVIOUS TEXT

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

REVISED TEXT

Approximately 45 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

SECTION 4.5 – Dose Justification

PREVIOUS TEXT

The dose chosen for this study is 1000 µg of GSK2269557 per day administered via a dry powder inhaler for a duration of 84 days (– 4 / + 2 days). This dose has been selected based on previous safety and tolerability data in man (healthy subjects and COPD subjects) as well as demonstration of target (PI3Kδ) inhibition by observed changes in

biomarkers. Together with an additional study to be run in parallel (PII116678), this dose of GSK2269557 is being dosed to subjects in PII116678 with an exacerbation of COPD, so it will be assumed for exposure predictions, unless otherwise stated, that these subjects will have a similar lung deposition, distribution and plasma exposure to that of the healthy volunteers. However it is accepted that these types of subjects may have reduced airway conductance and hence likely reduced deposition. This can be appropriately defined in this study based on the actual plasma exposures achieved.

Twice this dose level (2000 µg) using the same formulation has previously been given once daily to healthy male smokers for 14 days (study PII116617). There is also an ongoing study where a total daily dose of 1000 µg of GSK2269557 is administered to stable COPD subjects via a dry powder inhaler for 14 days (study PII115119) which at the time of writing of this protocol had successfully dosed 21 subjects on active treatment and collected pharmacokinetics (PK) samples for analysis out to 14 days.

The target effect compartment for PI3Kδ inhibition is the intracellular compartment of the immune cells resident in the lung tissue and lumen. GSK2269557 has a high potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL) which translates into an IC_{50} in a more complex system (PHA stimulated lung tissue) of approximately 120 ng/mL (or 2.5 ng/mL free unbound drug). Based on the measured steady-state cellular concentration of GSK2269557 collected at trough (24 h) from the lungs of healthy smokers at 2000 µg DPI (450 ng/mL) in the clinical study it is expected that at 1000 µg (225 ng/mL), concentrations will be sufficient and PI3Kδ inhibition maintained in the lung at ≥ 90% inhibition for 24 h.

Target PI3Kδ inhibition is based on a wide range of pharmacology experiments. Details of these as well as the pharmacokinetics and safety data can be found in the IB, [GlaxoSmithKline Document Number: 2012N141231_06].

REVISED TEXT

The dose chosen for this study is 700 µg of GSK2269557 per day administered via a dry powder ELLIPTA inhaler for a duration of 84 days (– 4 / + 2 days) and is equivalent to the dose of 1000 µg administered via DISKUS in terms of the dose deposited and systemic exposure.. This dose has been selected based on previous safety and tolerability data in man, obtained in healthy subjects, healthy smokers and COPD patients including patients suffering COPD exacerbations. Also dose selection is based on a healthy subjects study using the ELLIPTA™ DPI. It will be assumed for exposure predictions, unless otherwise stated, that patients suffering exacerbations will have a similar lung deposition, distribution and plasma exposure to that of the healthy volunteers. However it is accepted that these types of subjects may have reduced airway function and hence potentially reduced deposition. This can be appropriately defined in this study based on the actual plasma exposures achieved.

For DISKUS, twice this dose level (2000 µg) using the same formulation has previously been given once daily to healthy male smokers for 14 days (study PII116617). There is also an ongoing study where a total daily dose of 1000 µg of GSK2269557 is administered to stable COPD subjects via a dry powder inhaler for 14 days (study

PII115119) which at the time of writing of this protocol had successfully dosed 21 subjects on active treatment and collected pharmacokinetics (PK) samples for analysis out to 14 days.

The target effect compartment for PI3Kδ inhibition is the intracellular compartment of the immune cells resident in the lung tissue and lumen. GSK2269557 has a high potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL) which translates into an IC_{50} in a more complex system (PHA stimulated lung tissue) of approximately 120 ng/mL (or 2.5 ng/mL free unbound drug). Based on the measured steady-state cellular concentration of GSK2269557 collected at trough (24 h) from the lungs of healthy smokers at 2000 µg DPI (450 ng/mL) in the clinical study it is expected that at 1000 µg (225 ng/mL), concentrations will be sufficient and PI3Kδ inhibition maintained in the lung at ≥ 90% inhibition for 24 h.

Target PI3Kδ inhibition is based on a wide range of pharmacology experiments. Details of these as well as the pharmacokinetics and safety data can be found in the IB, [GlaxoSmithKline Document Number: 2012N141231_06].

SECTION 6.1 – Investigational Product and Other Study Treatment

PREVIOUS TEXT

	Study Treatment	
Product name:	GSK2269557	Placebo
Formulation description:	Lactose blend containing GSK2269557 in Diskus™ device	Lactose in Diskus device
Dosage form:	Dry powder for inhalation	Dry powder for inhalation
Unit dose strength(s)/Dosage level(s):	500 µg / blister	N/A
Route of Administration	Inhalation	Inhalation
Dosing instructions:	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.

REVISED TEXT

Study Treatment Name:	GSK2269557 ELLIPTA™ DPI (100 µg)	GSK2269557 ELLIPTA™ DPI (500 µg)	Placebo ELLIPTA™ DPI
Formulation description:	GSK2269557 blended with lactose and magnesium stearate	GSK2269557 blended with lactose and magnesium stearate	Lactose
Dosage formulation:	DPI	DPI	DPI
Unit dose strength(s)/Dosage level(s):	100 µg per blister	500 µg per blister	NA
Route of Administration:	Inhaled	Inhaled	Inhaled
Dosing instructions:	Inhale as directed	Inhale as directed	Inhale as directed
Physical description:	Dry white powder	Dry white powder	Dry white powder
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	Study Treatment will be labeled as required per country requirement.	Study Treatment will be labeled as required per country requirement.	Study Treatment will be labeled as required per country requirement.
Manufacturer	GSK	GSK	GSK

PREVIOUS TEXT

SECTION 6.2 – Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Central based randomisation will be used.

Subjects will be randomised to treatments A or B where:

A = Placebo

B = GSK2269557 1000 µg

A web based interactive response system will be used to assign subjects to treatment.

REVISED TEXT

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Central based randomisation will be used.

Subjects will be randomised to treatments A, B, C or D where:

A = Placebo

B = GSK2269557 1000 µg

C = Placebo via Ellipta

D = GSK2269557 700 µg via Ellipta

A web based interactive response system will be used to assign subjects to treatment.

PREVIOUS TEXT

SECTION 6.8 – Compliance with Study Treatment Administration

When subjects 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 subjects will be asked to complete a diary when dose administration takes place at home. The date, time and number of inhalations will be recorded. The compliance will be checked by the site staff at each planned visit.

A record of the number of Diskus inhalers dispensed to each subject and the number of actuation administered, read from the dose counter for each Diskus inhaler, must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

REVISED TEXT

When subjects 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 subjects will be asked to complete a diary when dose administration takes place at home. The date, time and number of inhalations will be recorded. The compliance will be checked by the site staff at each planned visit.

A record of the number of **ELLIPTA™** inhalers dispensed to each subject and the number of actuation administered, read from the dose counter for each **ELLIPTA™** inhaler, must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

PREVIOUS TEXT

SECTION 6.9 – Treatment of Study Treatment Overdose

For this study, any dose of GSK2269557 >2000 µg within a 22 hour time period will be considered an overdose.

GSK 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 subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2269557 can no longer be detected systemically (at least 14 days for GSK2269557)
3) obtain a plasma sample for pharmacokinetic (PK) analysis within 7 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 subject.

REVISED TEXT

For this study, any dose of GSK2269557 >2000 µg for DISKUS and >1400 µg for ELLIPTA within a 22 hour time period will be considered an overdose.

GSK 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 subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2269557 can no longer be detected systemically (at least 14 days for GSK2269557)
3) obtain a plasma sample for pharmacokinetic (PK) analysis within 7 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 subject.

PREVIOUS TEXT

SECTION 7.2 – Time and Events Table (Treatment Period)

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.

OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

13. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
14. Assessments do not need to be completed if screening assessments conducted within 48 hours
15. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
16. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

REVISED TEXT

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========					==========→	
Concomitant medication review	←==========					==========→	
Reliever usage	←==========					==========→	
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
ELLIPTA™ Inhaler Training	X						Training conducted by reviewing the Patient Information Leaflet with the subject (no device will be used). Additional training may be conducted at the discretion of the investigator
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	
Diary Card dispense and review at clinic	X		X	X	X	X	Refer to SRM for details.

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

17. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
18. Assessments do not need to be completed if screening assessments conducted within 48 hours
19. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
20. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

SECTION 9 – Statistical Considerations and Data Analyses

PREVIOUS TEXT

This study is designed to establish the PI3Kδ-dependent alterations in immune cell mechanisms related to neutrophil function as detected by changes in mRNA transcriptomics in samples of induced sputum from patients admitted with an exacerbation of COPD. The primary comparison will be between subjects treated with GSK2269557 in addition to standard of care, and subjects treated with placebo in addition to standard of care. In addition, treatment comparisons between subjects at baseline and subsequent time points will also be produced.

REVISED TEXT

This study is designed to establish the PI3Kδ-dependent alterations in immune cell mechanisms related to neutrophil function as detected by changes in mRNA transcriptomics in samples of induced sputum from patients admitted with an exacerbation of COPD. The primary comparison will be between subjects treated with GSK2269557 in addition to standard of care, and subjects treated with placebo in addition to standard of care. In addition, treatment comparisons between subjects at baseline and subsequent time points will also be produced. By first intent, the data from the different devices will be pooled and may also be investigated separately, full details will be specified in the RAP prior to unblinding.

SECTION 12.1 – Appendix 1 (Abbreviation and Trademarks)

Dry Powder Inhaler (DPI) included as an abbreviation within Appendix 1 of the Protocol Amendment.

PREVIOUS TEXT

12.1 Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
ECG	Electrocardiogram
FEV1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
GCP	ICH Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure

IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
PEF	Peak Expiratory Flow
PI3Kδ	Phosphoinositide 3-Kinase Delta
PK	Pharmacokinetic
QTcF	QT interval corrected using the Fridericia's formula
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SRM	Study Reference Manual
TLC	Total Lung Capacity
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
DISKUS	None

REVISED TEXT

12.1 Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
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CV	Cardiovascular
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DPI	Dry Powder Inhaler
FEV1	Forced Expiratory Volume in One Second
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FRI	Functional Respiratory Imaging
GCP	ICH Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
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PI3Kδ	Phosphoinositide 3-Kinase Delta

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DISKUS
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
None

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).

Compound Number: GSK2269557

Development Phase: IIA

Effective Date: 16-NOV-2016

Protocol Amendment Number: 03

Author (s): PPD (CCSE); PPD (CPSSO); PPD (Respiratory CEDD); PPD (Exp Biology); PPD (Clinical Statistics); PPD (CPMS); PPD (GCSP).

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N218070_00	2015-JUN-04	Original
2014N218070_01	2015-NOV-30	Amendment No. 1
Remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria and in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. It therefore is not valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.		
2014N218070_02	2016-JAN-26	Amendment No. 2
Increase the body mass index (BMI) range in the inclusion criteria from 18-32 kg/m^2 (inclusive) to 16- 35 kg/m^2 (inclusive). The original BMI range from 18-32 kg/m^2 is a typical range used in both healthy volunteer studies and general subject populations. The revised range is more appropriate for a COPD patient population.		
2014N218070_03	2016-NOV-16	Amendment No. 3
To remove photo toxicity from the protocol and to include minor administrative and clarification changes.		

SPONSOR SIGNATORY

PPD

16. 11. 16.

Tony Cahn
Head of Respiratory Discovery,
Respiratory R&D, Stevenage.

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
Secondary Medical Monitor					Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 201928

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

TABLE OF CONTENTS

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1. PROTOCOL SYNOPSIS FOR STUDY 201928

Rationale

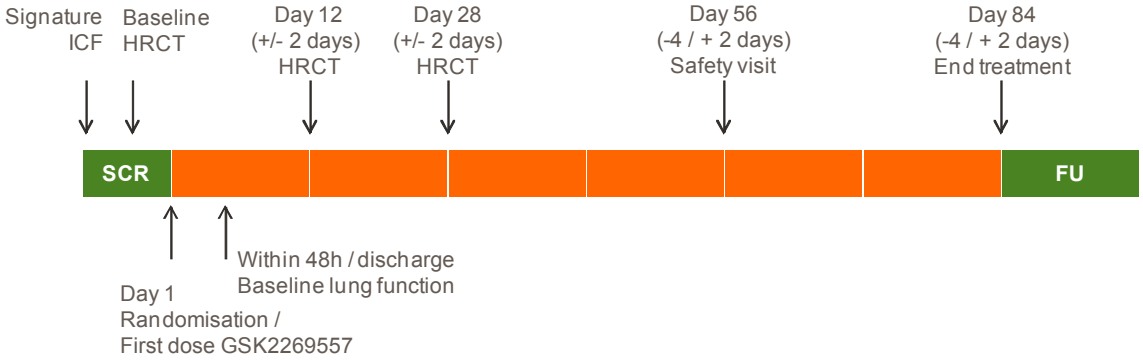
Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Haematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD.	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.	• PEF • Reliever usage • $FEV_{1\ and}$ FVC at clinic prior to sputum induction
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.

Objectives	Endpoints
exacerbation of COPD, compared to placebo.	
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment

Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual Chronic Obstructive Pulmonary Disease (COPD) medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The High-Resolution Computed Tomography (HRCT) scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (± 2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table. Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7-14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

Type and Number of Subjects

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected numbers of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

Analysis

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

2. INTRODUCTION

GSK2269557 is a potent and highly selective inhaled Phosphoinositide 3-Kinase Delta (PI3Kδ) inhibitor being developed as an anti-inflammatory and anti-infective agent for the treatment of inflammatory airways diseases.

2.1. Study Rationale

The purpose of this study is to evaluate specific alterations in immune cell mechanisms related to neutrophil function as detected by PI3Kδ-dependent changes in mRNA extracted from induced sputum in patients experiencing an exacerbation of COPD. In addition this study will also further evaluate the plasma PK and assess the safety of GSK2269557 administered to patients diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD). The efficacy of treatment with GSK2269557 will also be measured using functional respiratory imaging (FRI) and spirometry.

This study will also explore the pharmacodynamic effects of once daily repeat doses of inhaled GSK2269557 on cytokines, mediators and microbiome in induced sputum samples. These will be obtained from subjects at entry, during their exacerbation, and at additional time points over the 12 week treatment period. To understand patient efficacy, at entry, Day 12 and Day28 the sputum biomarker data will be correlated with computed tomography (CT).

2.2. Brief Background

PI3Kδ is a member of the Class IA family of phosphoinositides 3-kinases (PI3Ks) that convert the membrane phospholipid phosphatidylinositol 4,5-biphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is a second messenger in many cellular processes including cell growth, differentiation and migration. PI3Kδ has specific roles in mediating antigen receptor and cytokine signalling in T-cells, mast cells and B-cells [Okkenhaug, 2007] and roles in neutrophil chemotaxis and activation [Sadhu, 2003]. A PI3Kδ inhibitor has the potential to inhibit major cell types responsible for the inflammation associated with both COPD and asthma.

In COPD, tobacco smoke or other irritants activate epithelial cells and macrophages to release inflammatory mediators such as chemokines that attract neutrophils and T cells to the lungs. PI3Kδ is thought to play a role in a number of epithelial responses relevant for the development of COPD. Therefore a PI3Kδ inhibitor may be able to suppress a number of these processes [Kim, 2010]. A greater proportion of macrophages appear to be alternatively activated in COPD and their ability to phagocytose infective pathogens is reduced as a result of this alternative activation. PI3Kδ is one of the mediators involved in determining this alternative phenotype in macrophages and therefore it is proposed that inhibition of PI3Kδ might rebalance macrophage activation towards a classic phagocytic phenotype [Weisser, 2011] facilitating clearance of bacteria, a major cause of exacerbation in COPD. The neutrophil and T cell are the two major inflammatory cell types involved in the pathogenesis of COPD and both are targeted by PI3Kδ inhibitors.

GSK2269557 has demonstrated the ability to protect against and control bacterial infections in preclinical rodent models. This is coupled with recent observations that PI3Kδ inhibition leads to a correction in vitro of aberrant neutrophil chemotaxis directionality in the blood of COPD patients. Furthermore, a human point mutation which results in a constitutively activated version of PI3Kδ has recently been characterised where the majority of affected patients have recurrent lung infections with the same bacterial species which are seen in COPD patients and are known to drive exacerbations. Collectively these data suggest that repeat dosing with GSK2269557 could potentially reduce the impact of an acute exacerbation, or prevent the onset of a secondary bacterial exacerbation or recurrent exacerbation.

Proinflammatory cytokines were reduced by GSK2269557, both in preclinical rodent bacterial models, and COPD patient samples treated in vitro and in the study setting (PII115119).

GSK2269557 has been administered as single and repeat doses to healthy subjects as nebulized solution in the FTIH study PII115117 up to a dose of 6400 µg per day for 7 days. GSK2269557 has also been administered as single and repeat doses to healthy smokers as a dry powder formulation in study PII116617 up to a dose of 3000 µg as single dose and 2000 µg per day for 14 days. GSK2269557 has been well tolerated across the range of doses used. There is also an ongoing study (Study PII115119, non-reported) where a total daily dose of up to 2000 µg of GSK2269557 is being administered to stable COPD patients via a dry powder inhaler for 14 days in a two part study. Part A of this study has completed and Part B will characterise the steady-state (exposure) dose response following repeat inhaled doses of up to 2000µg for the same treatment duration. There is also an on-going larger clinical study PII116678 which is almost identical in design to 201928 using 1000 µg of GSK2269557 per day administered via a Diskus dry powder inhaler to patients diagnosed with an acute exacerbation of COPD. For simplicity study PII116678 does not capture induced sputum hence cannot analyse any changes in mRNA. The primary objective of the current study is to capture induced sputum to enable the mRNA analysis on a smaller cohort.

More information about the non-clinical and clinical studies is available in the GSK2269557 Investigator's Brochure (IB) GlaxoSmithKline Document Number 2012N141231_06.

2.2.1. Use of mRNA transcriptomics by Affymetrix

Analysis of changes in mRNA can be used to demonstrate alterations in biochemical pathways at the gene transcription level. This can be used to better understand the consequences of drug intervention on disease pathophysiology, and ultimately predict alterations which could translate to a positive clinical benefit for patients. Messenger RNA can be extracted from a variety of biological samples (including induced sputum and blood) taken from patients before and after drug dosing to show the impact a drug is having.

The advantage of using Affymetrix is the broad (~50k) gene set covered using this technology enabling great depth in exploring the biological consequences of drug intervention. This technology has been used in previous preclinical and clinical studies using GSK2269557 generating a fingerprint of PI3Kδ inhibition in disease. Importantly these approaches allow areas of complex PI3Kδ-dependent immune cell mechanisms and pathophysiology, specifically related to neutrophil function to be explored which are not easily quantified using other techniques.

2.2.2. Use of HRCT Endpoints to characterise Lung Function

High-resolution computed tomography (HRCT) scans provide a highly detailed insight into the structure and architecture of the respiratory system. A clear distinction can be made between the lung parenchyma, the intraluminal air and alveolar spaces up to the level of the smaller airways with a diameter of 1-2mm. To model dynamic information, low dose HRCT scans can be taken at two lung volumes: after deep inhalation (total lung capacity or TLC) and after normal expiration (functional residual capacity or FRC). The patient's breathing is monitored in real time during the scans to ensure the correct lung levels are scanned. Due to the natural contrast between the intraluminal air and the surrounding tissue, it is possible to attain a significant reduction in radiation dose (1-2 mSv per scan) compared to standard CT protocols (>4 mSv per scan) by reducing the tube current and the voltage. Depending on the patient's weight, a 6- to 10-fold reduction can be obtained per scan without losing image quality. As a comparison, in the USA, the average annual background radiation exposure is 6.2 mSv and a transatlantic flight results in 0.07 mSv exposure.

The high resolution images allow for a three dimensional reconstruction of the airway tree and vasculature by applying segmentation principles. These three dimensional models can be used to measure airway dimensions as well as potentially allowing the phenotyping of patients by disease severity. The three dimensional computer reconstructions can be used for fluid dynamic modelling. This method is used to simulate flow through these airway models and determine the typical flow characteristics such as local pressure drops, velocities and resistance. It can also be used to predict particle deposition in the airways of these patients when using inhaled drug products.

This method consisting of 2 low dose HRCT scans at several time points has previously been used successfully in clinical trials involving COPD patients [De Backer, 2011; De Backer, 2012; De Backer, 2014; Goldin, 1999].

3. OBJECTIVE(S) AND ENDPOINT(S)

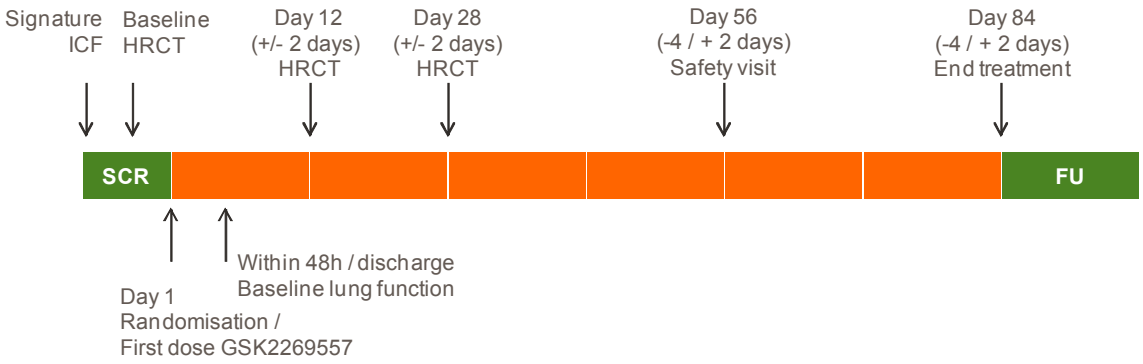
Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Hematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD, compared to placebo	• PEF, Reliever usage. • FEV_1 and FVC at clinic prior to sputum induction.
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.

Objectives	Endpoints
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment.

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual COPD medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



4.2. Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The HRCT scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (±2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table (Section 7.1). Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7 to 14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

4.3. Type and Number of Subjects

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

4.4. Design Justification

This study will include a placebo control to allow for a valid evaluation of the pharmacodynamic endpoints and adverse events attributable to treatment versus those

independent of treatment. Subjects will also receive standard of care for their exacerbation and throughout the study.

4.5. Dose Justification

The dose chosen for this study is 1000 µg of GSK2269557 per day administered via a dry powder inhaler for a duration of 84 days (– 4 / + 2 days). This dose has been selected based on previous safety and tolerability data in man (healthy subjects and COPD subjects) as well as demonstration of target (PI3Kδ) inhibition by observed changes in biomarkers. Together with an additional study to be run in parallel (PII116678), this dose of GSK2269557 is being dosed to subjects in PII116678 with an exacerbation of COPD, so it will be assumed for exposure predictions, unless otherwise stated, that these subjects will have a similar lung deposition, distribution and plasma exposure to that of the healthy volunteers. However it is accepted that these types of subjects may have reduced airway conductance and hence likely reduced deposition. This can be appropriately defined in this study based on the actual plasma exposures achieved.

Twice this dose level (2000 µg) using the same formulation has previously been given once daily to healthy male smokers for 14 days (study PII116617). There is also an ongoing study where a total daily dose of 1000 µg of GSK2269557 is administered to stable COPD subjects via a dry powder inhaler for 14 days (study PII115119) which at the time of writing of this protocol had successfully dosed 21 subjects on active treatment and collected pharmacokinetics (PK) samples for analysis out to 14 days.

The target effect compartment for PI3Kδ inhibition is the intracellular compartment of the immune cells resident in the lung tissue and lumen. GSK2269557 has a high potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL) which translates into an IC_{50} in a more complex system (PHA stimulated lung tissue) of approximately 120 ng/mL (or 2.5 ng/mL free unbound drug). Based on the measured steady-state cellular concentration of GSK2269557 collected at trough (24 h) from the lungs of healthy smokers at 2000 µg DPI (450 ng/mL) in the clinical study it is expected that at 1000 µg (225 ng/mL), concentrations will be sufficient and PI3Kδ inhibition maintained in the lung at ≥ 90% inhibition for 24 h.

Target PI3Kδ inhibition is based on a wide range of pharmacology experiments. Details of these as well as the pharmacokinetics and safety data can be found in the IB, [GlaxoSmithKline Document Number: 2012N141231_06].

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2269557 can be found in the IB [GlaxoSmithKline Document Number 2012N141231_06]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm	A general risk with Inhaled treatment	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on screening, Day 12 and Day 28 visits) at are required throughout the study for the functional imaging protocol	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be approximately 12mSv. Final radiation dose will be dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk). The outcomes of this study will provide information which would produce advances in knowledge, leading to a potential health benefit in the future for patients in this target population. The CT may also provide information for the patients general clinical

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation.	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the opinion of the Investigator, it is considered safe to do so.

4.6.2. Benefit Assessment

The outcomes of this study will provide information which will produce advances in knowledge of the pathophysiology of COPD exacerbations, leading to a potential health benefit in the future for patients in this target population. The CT scan may also provide information for the patient's general clinical management.

4.6.3. Overall Benefit:Risk Conclusion

The overall benefit:risk is considered to be positive. There is an opportunity to determine if there may be a new drug developable for the treatment of acute exacerbations of COPD which has not seen any new treatments recently. The scientific value in obtaining functional CT information on the anatomy and pathophysiology of COPD exacerbations and how the lung responds to therapy will be extremely valuable to the wider clinical community and justifies the limited radiation exposure (maximum 12 mSv in total) from

the CT scan procedures. The CT will also be useful to provide clinical information about the patient for the patient's physician and contribute to clinical management.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number: 2012N141231_06]

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

[1] AGE
• Between 40 and 80 years of age inclusive, at the time of signing the informed consent.
[2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
• The subject has a confirmed and established diagnosis of COPD, as defined by the GOLD guidelines for at least 6 months prior to entry. • The subject is able to produce >100 mg of sputum at screening for processing, (ie, total weight of sputum plugs.). • The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted documented in the last 5 years. • Disease severity: Acute exacerbation of COPD requiring an escalation in therapy to include both corticosteroid and antibiotics. Acute exacerbation to be confirmed by an experienced physician and represent a recent change in at least two major and one minor symptoms, one major and two minor symptoms, or all 3 major symptoms. 1. Major symptoms: • Subjective increase in dyspnea • Increase in sputum volume • Change in sputum colour 2. Minor symptoms: • Cough

- Wheeze
- Sore throat

- The subject is a smoker or an ex-smoker with a smoking history of at least 10 pack years (pack years = (cigarettes per day smoked/20 x number of years smoked)).

[3] WEIGHT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 16 – 35 kg/m^2 (inclusive).

[4] SEX

- Male
- Female subject : is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

1. Non-reproductive potential defined as:

Pre-menopausal females with one of the following:

Documented tubal ligation

Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion

Hysterectomy

Documented Bilateral Oophorectomy

Postmenopausal defined as 12 months of spontaneous amenorrhea. Females whose menopausal status is in doubt will be required to use, or have been using, one of the highly effective contraception methods as specified below from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

2. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher,

2007a]

3. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
4. Injectable progestogen [Hatcher, 2007a]
5. Contraceptive vaginal ring [Hatcher, 2007a]
6. Percutaneous contraceptive patches [Hatcher, 2007a]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
8. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Specific inclusion criteria for Male subjects with female partners of reproductive potential is outlined below:

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until after the completion of the follow up visit.

3. Vasectomy with documentation of azoospermia.
4. Male condom plus partner use of one of the contraceptive options below:

Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label

Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]

Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a]

Contraceptive vaginal ring [Hatcher, 2007a]

Percutaneous contraceptive patches [Hatcher, 2007a]

5. These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

[5] INFORMED CONSENT
• Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

• To avoid recruitment of subjects with a severe COPD exacerbation, the presence of any one of the following severity criteria will render the subject ineligible for inclusion in the study:
  • Need for invasive mechanical ventilation (short term (< 48h) NIV or CPAP is acceptable)
  • Haemodynamic instability or clinically significant heart failure
  • Confusion
  • Clinically significant pneumonia, identified by chest X-ray at screening, and as judged by the Investigator.
• Subjects who have current medical conditions or diseases that are not well controlled and, which as judged by the Investigator, may affect subject safety or influence the outcome of the study. (Note: Patients with adequately treated and well controlled concurrent medical conditions (e.g. hypertension or NIDDM) are permitted to be entered into the study).
• Subject has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the subject or affect the interpretation of the results.
• ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
• A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the exclusion criteria, outside of the reference range for the population being studied may be included if the Investigator [in consultation with the GSK Medical Monitor if required] documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
• Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
• ECG indicative of an acute cardiac event (e.g. Myocardial Infarction) or demonstrating a clinically significant arrhythmia requiring treatment.
• QTcF > 450 msec or QTcF > 480 msec in subjects with Bundle Branch Block, based on single QTcF value.
• Subjects who have undergone lung volume reduction surgery.

[2] CONCOMITANT MEDICATIONS
• Subject is currently on chronic treatment with macrolides or long term antibiotics. • Subject is being treated with long term oxygen therapy - LTOT (> 15 hours/day). • The subject has been on chronic treatment with anti-Tumour Necrosis Factor (anti-TNF), or any other immunosuppressive therapy (except corticosteroid) within 60 days prior to dosing.

[3] RELEVANT HABITS
• History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >28 units for males or >21 units for 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.

[4] CONTRAINDICATIONS
• History of sensitivity to any of the study medications, or components thereof (such as lactose) or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

[5] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
• A known (historical) positive test for HIV antibody. • Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. NOTE: Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor. • Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. • The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). • Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal

set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria Protocol Deviations, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn should complete all the assessments planned, if possible. Subjects who are withdrawn **on a study clinic visit** after randomization should complete all the safety related assessment for that visit which includes at minimum, vital sign, lab assessments (if deem necessary by the PI), AE/SAEs, concomitant medication(s) and ECG. A Follow up Visit should be scheduled 7-14 days post last dose.

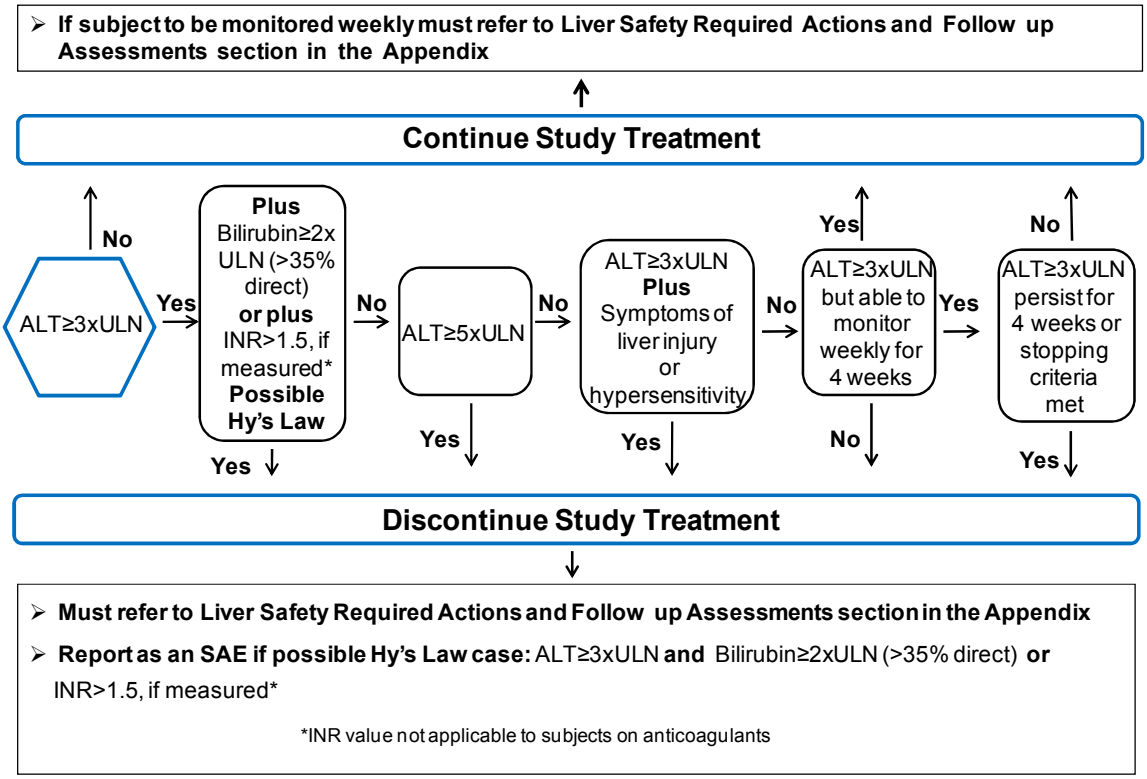
Subjects who are withdrawn **in between study clinic visits** should complete the unscheduled visit and complete all the safety related assessment at minimum which includes, vital sign, lab assessments (if deem necessary by the PI), AEs/SAEs, concomitant medication(s) and ECG. A Follow up Visit should be scheduled 7-14 post last dose.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.1.1. Study Treatment Restart or Re-challenge

Study treatment restart or re-challenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.2. QTc Stopping Criteria

- QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. For example, if an ECG (Electrocardiogram) demonstrates a prolonged QTcF interval, obtain two more ECGs and use the averaged QTcF values of the three ECGs to determine whether the patient should be discontinued from the study.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

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

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

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

5.4.3. Other Stopping Safety Criteria

For an individual study participant, stopping criteria include, but are not limited to:

Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests, spirometry assessments, etc), as judged by the Principal Investigator in consultation with the Medical Monitor if necessary.

Treatment failure or recurrent exacerbation does **not** mandate withdrawal from the study, unless there is a safety concern as judged by the Investigator, in consultation with the Medical Monitor if necessary.

Subjects should be withdrawn from the study if confusion, acute respiratory acidosis (pH < 7.30), or need for invasive mechanical ventilation occurs.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment	
Product name:	GSK2269557	Placebo
Formulation description:	Lactose blend containing GSK2269557 in Diskus™ device	Lactose in Diskus device
Dosage form:	Dry powder for inhalation	Dry powder for inhalation
Unit dose strength(s)/Dosage level(s):	500 µg / blister	N/A
Route of Administration	Inhalation	Inhalation
Dosing instructions:	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.

6.2. Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Central based randomisation will be used.

Subjects will be randomised to treatments A or B where:

A = Placebo

B = GSK2269557 1000 µg

A web based interactive response system will be used to assign subjects to treatment.

6.3. Planned Dose Adjustments

If adverse events, unrelated to COPD exacerbation, which are of moderate or severe intensity and are consistent across subjects in the group, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK2269557, are observed in more than 30% of the subjects then the study will be halted and no further subject will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the Ethics Committees will then take place prior to any resumption of dosing. If the above is observed consideration may be given to reducing the dose of GSK2269557 to 500 µg O.D.

6.4. Subject Specific Dose Adjustment Criteria

There are no subject specific dose adjustment criteria.

6.5. Blinding

This will be a double blind study and the following will apply.

- The investigator or treating physician may un-blind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** un-blinding the subject's treatment assignment.
- If GSK personnel are not contacted before the un-blinding, the investigator must notify GSK as soon as possible after un-blinding.
- The date and reason for the un-blinding must be fully documented in the Case Report Form (CRF)
- A subject will be withdrawn if the subject's treatment code is un-blinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the un-blinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may un-blind the treatment assignment for any subject with a Serious Adverse Event (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 subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects 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 labelled 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 (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for 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.

6.8. Compliance with Study Treatment Administration

When subjects 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 subjects will be asked to complete a diary when dose administration takes place at home. The date, time and number of inhalations will be recorded. The compliance will be checked by the site staff at each planned visit.

A record of the number of Diskus inhalers dispensed to each subject and the number of actuation administered, read from the dose counter for each Diskus inhaler, must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.9. Treatment of Study Treatment Overdose

For this study, any dose of GSK2269557 >2000 µg within a 22 hour time period will be considered an overdose.

GSK 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 subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2269557 can no longer be detected systemically (at least 14 days for GSK2269557)
3) obtain a plasma sample for pharmacokinetic (PK) analysis within 7 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 subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Any clinical abnormalities identified during the conduct of the study will be locally managed by the Investigator.

6.11. Lifestyle and/or Dietary Restrictions

- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.
- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit, and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study and in such case, subjects should be advise to discontinue their own ventolin and use the study ventolin and aerochamber provided for the duration of the study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

6.12.2. Prohibited Medications and Non-Drug Therapies

Regular or chronic treatment with medications that are considered strong inhibitors of CYP3A4 or CYP2D6 are not permitted. This includes anti-epileptic treatments, macrolide antibiotics, oral antifungal treatments (single doses and courses up to 7 days are allowed) and anti-tuberculous therapy. These medications must all have been stopped at least 14 days prior to first dose.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table (Screening and Follow Up Visits)

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Informed consent	X		
Demography	X		
Inclusion and exclusion criteria	X		
Full physical exam, including height and weight	X		
Brief physical examination, including weight		X	
Chest X-Ray	X		To be done before baseline HRCT to exclude significant pneumonia and other incidental serious underlying pathology.
Medical history (includes substance usage and Family history of premature CV disease)	X		Substances: Drugs, Alcohol, tobacco via history. No drug, alcohol screening is required.
Past and current medical conditions (including cardiovascular medical history and therapy history)	X		
Laboratory assessments (include Hematology and biochemistry)[1]	X	X	Historical values analysed by local lab to be used for eligibility assessment. Another sample must be collected and sent to central lab as soon as informed consent is obtained.
Hep B and Hep C screen[2]	X		
Urine pregnancy test (only WCBP)	X		Before conducting the HRCT. Done locally at the site.
12-lead ECG	X	X	Single assessment
Vital signs	X	X	Single assessment
HRCT (at TLC and FRC)	X		Within 48 h of diagnosis, if subject otherwise eligible. Includes electronic monitoring of breathing (if applicable). Baseline HRCT will be reviewed by the local site's radiologist to identify any significant occurring underlying medical conditions that require further clinical management or monitoring.
Induced Sputum[3]	X[4]		To include sputum culture pre-first dose. Culture to be done by the local site laboratory.
Blood sample for mRNA Analysis	X[4]		Collected at any time on specified days
AE/SAE collection and review		X	

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Concomitant medication review	X	X	

1. Due to the short screening window, central laboratory analysis results will not be available on time. Therefore the local laboratory results should be used for eligibility assessment (to exclude severe subjects and underlying medical conditions). If local laboratory results are already available from diagnosis of current exacerbation, there is no need to take another sample for local analysis. A sample for central laboratory analysis should also be obtained. See Section 7.8.6 for further details.
2. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required. Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor.

3. Induced sputum collection may be attempted on several occasions if an adequate sample is not produced at the first attempt.
4. To be collected at any time point before randomisation.

7.2. Time and Events Table (Treatment Period)

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	
Diary Card dispense and review at clinic	X		X	X	X	X	Refer to SRM for details.

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========					==========→	Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

1. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
2. Assessments do not need to be completed if screening assessments conducted within 48 hours
3. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
4. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

7.3. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

If they are being utilised in the study, Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

7.4. Biomarker(s)/Pharmacodynamic Markers

7.4.1. Pharmacodynamic Biomarkers in Sputum

- Collect sputum induction samples at the time-points shown in the time and events table (Section 7.1).
- The sputum induction collection process will follow local standard procedures and guidelines outlined in the SRM.
- The collection of induced sputum may be attempted on several occasions if an adequate sample is not produced at the first attempt.
- Further information on collection, processing, storage and shipping procedures are provided in the SRM.

7.4.2. mRNA in blood

- Collect 2.5 mL of blood into a PAXgene mRNA tube.

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

7.5. Patient diary

The subjects will be provided with a diary to record the following data when at home:

- Time and date of each dose administration and number of inhalations.
- Adverse Events and concomitant medications taken (including daily rescue medication – if used and how many times used).

- PEF from a handheld device. The best/highest result is recorded.

Changes in Health and details of any concomitant medications as well as PEF assessment details will be collected in the paper diaries and later transcribed into the CRF.

7.6. Genetics

Information regarding genetic research is included in Appendix 3.

7.7. Efficacy

7.7.1. Functional Respiratory Imaging

- A CT scan with a low radiation protocol at FRC and TLC will be conducted as listed in the Time and Events Table (Section 7.1). The same scanner should be used for baseline and post-treatment scans for an individual subject.
- A urine pregnancy test should be performed before the CT scan in female subjects of childbearing potential.
- Further information is provided in the SRM.

7.7.2. FEV_1 and FVC

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. These will be recorded as absolute values. The best/highest result is recorded.

- Further details are provided in the SRM.

7.7.3. Peak Expiratory Flow PEF

- PEF measurements will be taken (in triplicate) daily in the morning before dose administration, as soon as it is safe for the subject to do so. The best/highest result is recorded.
- Subjects will be provided with a handheld device.
- Further details are provided in the SRM.

7.8. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.8.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.8.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.8.1.3), at the time-points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.8.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.8.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

7.8.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

7.8.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless they meet the definition of an SAE as defined in Appendix 4 Exacerbations that meet the definition of an SAE will be recorded on the appropriate eCRF section and should be reported to GSK.

Medications used to treat a COPD exacerbation will be recorded in the exacerbation eCRF

7.8.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.8.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until the follow-up visit
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.8.3. Physical Exams

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

7.8.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.
- Three readings of blood pressure and pulse rate will be taken
- First reading should be rejected
- Second and third readings should be averaged to give the measurement to be recorded in the CRF.

7.8.5. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at screening and at each other timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

7.8.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Historical values (if the assessment was conducted as part of the standard of care) for blood gases, blood culture and sputum culture may also be collected if available.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Table 1 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential:</u></td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose (non fasted)</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
<tr><td>CRP</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>• Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)</td></tr>
</table>

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 5.4.1 and Appendix 2
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Hematology and clinical chemistry at screening for excluding subjects with severe disease and uncontrolled medical conditions. The results of each test must be entered into the CRF.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Hematology, clinical chemistry and additional parameters to be tested are listed in Table 1.

7.9. Pharmacokinetics

7.9.1. Blood Sample Collection

A 2 mL blood samples for pharmacokinetic (PK) analysis of GSK2269557 will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.9.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK2269557 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for GSK2269557 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK/Scinovo, GlaxoSmithKline protocol.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

This study is designed to establish the PI3Kδ-dependent alterations in immune cell mechanisms related to neutrophil function as detected by changes in mRNA transcriptomics in samples of induced sputum from patients admitted with an exacerbation of COPD. The primary comparison will be between subjects treated with GSK2269557 in addition to standard of care, and subjects treated with placebo in addition to standard of care. In addition, treatment comparisons between subjects at baseline and subsequent time points will also be produced.

9.1. Sample Size Considerations

The sample size for this study has been based on feasibility. The sample size of 30 subjects completing the trial, with approximately 15 of which will receive GSK2269557 and 15 will receive placebo, is expected to be sufficient to provide a meaningful estimate of the mRNA alterations within the lungs.

Previous studies with similar sample size populations have yielded significant fold-changes (fold-change>1.5 and $p<0.05$) in immune cell mechanisms using the changes in mRNA transcriptomics.

Study Name	Sample	Study Design	Number of Subjects	Number of Differential probesets FC = >= 1.5, Pval <= 0.05	Notes
PII115117 FTIH Healthy Smoker nebulised GSK2269557	Sputum	Sputum N=12 3-way x-over placebo 400ug, 6400ug	12 (9 with all data points)	57 probesets change with both doses = 44 Genes	Gene changes relate predominantly to a down regulation of infection and inflammation responses. Link to Haemophilus influenzae and Moraxella catarrhalis infection biology – Identified prior to knowledge of Activated PI3Kδ Syndrome phenotype
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Sputum	Ex vivo Sputum incubated with GSK2269557 sampled at 6hrs (Sputum producers)	15 Subjects	490 probesets change vs vehicle control = 295 genes (of which 43 are dysregulated in COPD disease vs Healthy comparison)	43 genes altered in COPD and positively modulated by PI3Kδi GSK2269557. Biological themes in signature: Pro-cell movement/migration and cell viability, anti-apoptotic. Additionally link to B/T cell function. Signature supports GSK2269557 correction of neutrophil migration
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at 6hrs (Sputum	15 Subjects	19 probesets change vs vehicle control = 15 genes	Infection and inflammation associated genes
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at	15 Subjects	30 probesets change vs vehicle control = 25 genes	Infection and inflammation associated genes

9.1.1. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed in this study.

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Screened	• All subjects who were screened.	• Study Population
All subject	• All randomised subjects who receive at least one dose of the study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Pharmacodynamics • Safety • Efficacy
Pharmacokinetic	• Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.	• PK

9.2.2. Interim Analysis

No interim analyses will be performed.

9.3. Key Elements of Analysis Plan

9.3.1. Primary Analyses

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

Further details around the analysis of the mRNA data will be provided in the RAP.

9.3.2. Secondary Analyses

All secondary analyses will be described in full prior to unblinding in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)

- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all

relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
ECG	Electrocardiogram
FEV1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
GCP	ICH Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
PEF	Peak Expiratory Flow
PI3Kδ	Phosphoinositide 3-Kinase Delta
PK	Pharmacokinetic
QTcF	QT interval corrected using the Fridericia's formula
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SRM	Study Reference Manual
TLC	Total Lung Capacity
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DISKUS

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **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 subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (refer to Appendix 2). • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained 7 days after last dose[5] • 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

treatment and may continue subject in the study for any protocol specified follow up assessments	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form
MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • 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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, 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 subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. PK sample may not be required for subjects 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 blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.3. Appendix 3: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- COPD susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to

the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where 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.

12.4.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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 disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are 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

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject'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 instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject 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 the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication

Pregnancy information on female partner of male study subjects

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks 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: Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7: Protocol Amendment Changes

Protocol Amendment #1 Changes

The amendment was created to remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria (European Community of Coal and Steel and European Respiratory Society Global Lung Function Initiative reference equations (Quanjer 2012) in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. As a result it may not be valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.

List of specific changes:

Page 22, Inclusion Criteria (#2 – Type of Subject and Diagnosis Including Disease Severity) - Third Bullet.

PREVIOUS TEXT

- The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted. Predictions should be according to the European Community of Coal and Steel (ECCS) equations OR the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012] and documented in the last 5 years.

REVISED TEXT

- The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted documented in the last 5 years.

Page 40, Section 7.7.2 (FEV_1 and FVC)

PREVIOUS TEXT

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. Predicted values will be based upon the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012].

REVISED TEXT

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. These will be recorded as absolute values. The best/highest result is recorded.

Page 54 – References

PREVIOUS TEXT

De Backer J, Vos W, Vinchurkar S, Van Holsbeke C, Poli, G, Claes R et al. The Effect of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Fundtional Respiratory Imaging. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:1-12.

De Backer LA, Vos WG, Salgado R, De Backer JW, Devoldr A, Verhulst SL et al. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD. *International Journal of COPD.* 2011;6:637-646.

De Backer Lieve A, Vos Wim, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. *Eur Respir J.* 2012;40:298-305.

GlaxoSmithKline Document Number 2012N141231_06: GSK2269557 Investigator's Brochure. Report Date 12-FEB-2015.

Goldin J, Tashkin D, Kleerup E, Greaser MS, Haywood U, Sayre J et al. Comparative effects of hydrofluoroalkane and chloroflurocarbon beclomethasone dipropionate inhalation on small airways: Assessment with functional helical thin-section computed tomography. *J Allergy Clin Immunol.* 1999;104 #6:S258-S267.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(a):24. Table 3-2.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(b): 28.

ICRP. 2007 Recommendation of the International Commission on Radiological Protection. *ICRP Publication 103.* 2007;37:2-4.

Kim SR, Lee KS, Park HS, et al. HIF -1 alpha inhibition ameliorates an allergic airway disease via VEGF suppression in bronchial epithelium. *Eur J Immunol.* 2010;40 (10):2858-69.

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Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI13K delta in neutrophil inflammatory responses. *Biochem Biophys Res Commun.* 2003 Sep 5;308 (4):764-9.

Weisser SB, McLarren KW, Voglmaier B, et al. Alternative activation of macrophages by IL-4 requires SHIP degradation. *Eur J Immunol.* 2011;41(6):1742-53.

REVISED TEXT

De Backer J, Vos W, Vinchurkar S, Van Holsbeke C, Poli, G, Claes R et al. The Effect of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Fundtional Respiratory Imaging. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:1-12.

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Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI13K delta in neutrophil inflammatory responses. *Biochem Biophys Res Commun.* 2003 Sep 5;308 (4):764-9.

Weisser SB, McLarren KW, Voglmaier B, et al. Alternative activation of macrophages by IL-4 requires SHIP degradation. *Eur J Immunol.* 2011;41(6):1742-53.

Protocol Amendment #2 Changes

This amendment was created to widen the Body Mass Index (BMI) range at the screening visit as the propose range from 16 – 35 kg/m^2 would be appropriate for the COPD subject population.

List of specific changes:

Page 22, Inclusion Criteria (#3 – Weight).

PREVIOUS TEXT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 18 – 32 kg/m^2 (inclusive).

REVISED TEXT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 16 – 35 kg/m^2 (inclusive).

Protocol Amendment #3 Changes

This amendment was created to remove the photo toxicity from the protocol as a result of the updated Investigator Brochure, Version 7.0, August16, 2016. It also contains minor administrative and clarification changes.

List of specific changes:

PREVIOUS TEXT

Section 4.6.1 (Table) – Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm	A general risk with Inhaled treatment	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Potential photosensitivity	In the absorption spectrum for GSK2269557 there are peaks at the boundary of the ultraviolet (UV) light [UVA/UVB] region with a lambda max at 320 nm (molar extinction coefficient 43800 L/Mol/cm), with smaller peaks at 305 nm and 332 nm.	Subjects will be advised to take UV protection measures (see Section 6.11).
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	screening, Day 12 and Day 28 visits) at are required throughout the study for the functional imaging protocol	approximately 12mSv. Final radiation dose will be dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk). The outcomes of this study will provide information which would produce advances in knowledge, leading to a potential health benefit in the future for patients in this target population. The CT may also provide information for the patients general clinical management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation.	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		opinion of the Investigator, it is considered safe to do so.

REVISED TEXT

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm	A general risk with Inhaled treatment	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on screening, Day 12 and Day 28 visits) at are required throughout the study for the functional imaging protocol	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be approximately 12mSv. Final radiation dose will be dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk). The outcomes of this study will

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		provide information which would produce advances in knowledge, leading to a potential health benefit in the future for patients in this target population. The CT may also provide information for the patients general clinical management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation.	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the opinion of the Investigator, it is considered safe to do so.

PREVIOUS TEXT

Apply to **ALL** sections with reference to IB, [GlaxoSmithKline Document Number: 2012N141231_**04**].

REVISED TEXT

Replace with:

IB, [GlaxoSmithKline Document Number: 2012N141231_**06**].

PREVIOUS TEXT

SECTION 5.4 – Withdrawal/Stopping Criteria

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn should complete the assessments planned for the follow up visit.

REVISED TEXT

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn should complete all the assessments planned, if possible. Subjects who are withdrawn **on a study clinic visit** after randomization should complete all the safety related assessment for that visit which includes at minimum, vital sign, lab assessments (if deem necessary by the PI), AE/SAEs, concomitant medication(s) and ECG. A Follow up Visit should be scheduled 7-14 days post last dose.

Subjects who are withdrawn **in between study clinic visits** should complete the unscheduled visit and complete all the safety related assessment at mininum which includes, vital sign, lab assessments (if deem necessary by the PI), AEs/SAEs, concomitant medication(s) and ECG. A Follow up Visit should be scheduled 7-14 post last dose.

PREVIOUS TEXT

SECTION 6.11 – Lifestyle and/or Dietary Restrictions

- Subjects must not sunbathe or use a tanning device (e.g. sunbed or solarium) whilst taking the study medication and until at least 2 weeks after their last dose. Subjects are to be advised that they should cover exposed areas of skin (e.g. use sun hat, long sleeves) and use a broad spectrum UVA/UVB sunscreen (SPF ≥30) on exposed areas of skin when outdoors.
- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.
- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

REVISED TEXT

- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.
- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

PREVIOUS TEXT

SECTION 6.12.1 – Permitted Medications and Non-Drug Therapies

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit, and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free

use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

REVISED TEXT

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit, and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study and in such case,subjects should be advise to discontinue their own ventolin and use the study ventolin and aerochamber provided for the duration of the study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

PREVIOUS TEXT

SECTION 7.2 – Time and Events Table (Treatment Period)

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

5. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
6. Assessments do not need to be completed if screening assessments conducted within 48 hours
7. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
8. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

REVISED TEXT

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	
Diary Card dispense and review at clinic	X		X	X	X	X	Refer to SRM for details.

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

9. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
10. Assessments do not need to be completed if screening assessments conducted within 48 hours
11. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
12. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

PREVIOUS TEXT

SECTION 11 – References

GlaxoSmithKline Document Number 2012N141231_04: GSK2269557 Investigator's Brochure. Report Date 12-FEB-2015.

REVISED TEXT

GlaxoSmithKline Document Number 2012N141231_06: GSK2269557 Investigator's Brochure. Report Date 16-AUG-2016.

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).

Compound Number: GSK2269557

Development Phase: IIA

Effective Date: 26-JAN-2016

Protocol Amendment Number: 02

Author (s): PPD (CCSE); PPD (CPSSO); PPD (Respiratory CEDD); PPD (Exp Biology); PPD (Clinical Statistics); PPD (CPMS); PPD (GCSP).

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N218070_00	2015-JUN-04	Original
2014N218070_01	2015-NOV-30	Amendment No. 1
Remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria and in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. It therefore is not valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.		
2014N218070_02	2016-JAN-26	Amendment No. 2
Increase the body mass index (BMI) range in the inclusion criteria from 18-32 kg/m^2 (inclusive) to 16- 35 kg/m^2 (inclusive). The original BMI range from 18-32 kg/m^2 is a typical range used in both healthy volunteer studies and general subject populations. The revised range is more appropriate for a COPD patient population.		

SPONSOR SIGNATORY

PPD

26-JAN-2016

Peter Phillips
Head of Respiratory Discovery
Medicine

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
Secondary Medical Monitor					Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

PROTOCOL AGREEMENT PAGE

For protocol 201928

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201928

Rationale

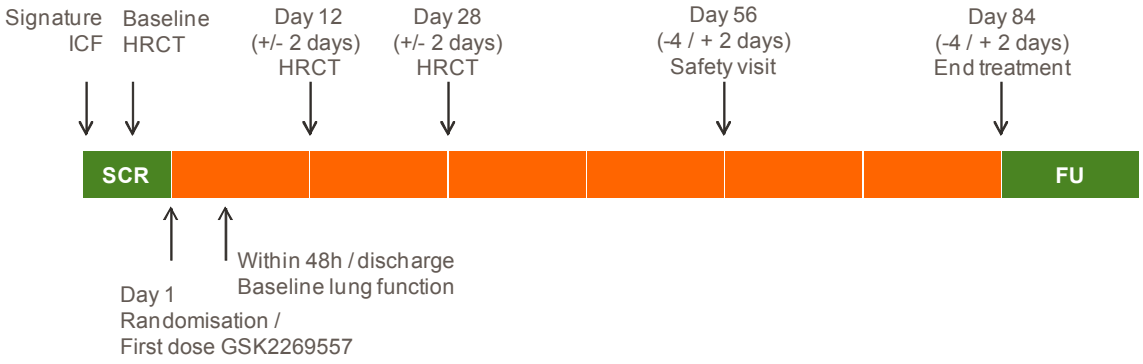
Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Haematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD.	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.	• PEF • Reliever usage • $FEV_{1\ and}$ FVC at clinic prior to sputum induction
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to

Objectives	Endpoints
inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment

Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual Chronic Obstructive Pulmonary Disease (COPD) medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The High-Resolution Computed Tomography (HRCT) scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (± 2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table. Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7-14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

Type and Number of Subjects

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected numbers of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

Analysis

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

2. INTRODUCTION

GSK2269557 is a potent and highly selective inhaled Phosphoinositide 3-Kinase Delta (PI3Kδ) inhibitor being developed as an anti-inflammatory and anti-infective agent for the treatment of inflammatory airways diseases.

2.1. Study Rationale

The purpose of this study is to evaluate specific alterations in immune cell mechanisms related to neutrophil function as detected by PI3Kδ-dependent changes in mRNA extracted from induced sputum in patients experiencing an exacerbation of COPD. In addition this study will also further evaluate the plasma PK and assess the safety of GSK2269557 administered to patients diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD). The efficacy of treatment with GSK2269557 will also be measured using functional respiratory imaging (FRI) and spirometry.

This study will also explore the pharmacodynamic effects of once daily repeat doses of inhaled GSK2269557 on cytokines, mediators and microbiome in induced sputum samples. These will be obtained from subjects at entry, during their exacerbation, and at additional time points over the 12 week treatment period. To understand patient efficacy, at entry, Day 12 and Day28 the sputum biomarker data will be correlated with computed tomography (CT).

2.2. Brief Background

PI3Kδ is a member of the Class IA family of phosphoinositides 3-kinases (PI3Ks) that convert the membrane phospholipid phosphatidylinositol 4,5-biphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is a second messenger in many cellular processes including cell growth, differentiation and migration. PI3Kδ has specific roles in mediating antigen receptor and cytokine signalling in T-cells, mast cells and B-cells [Okkenhaug, 2007] and roles in neutrophil chemotaxis and activation [Sadhu, 2003]. A PI3Kδ inhibitor has the potential to inhibit major cell types responsible for the inflammation associated with both COPD and asthma.

In COPD, tobacco smoke or other irritants activate epithelial cells and macrophages to release inflammatory mediators such as chemokines that attract neutrophils and T cells to the lungs. PI3Kδ is thought to play a role in a number of epithelial responses relevant for the development of COPD. Therefore a PI3Kδ inhibitor may be able to suppress a number of these processes [Kim, 2010]. A greater proportion of macrophages appear to be alternatively activated in COPD and their ability to phagocytose infective pathogens is reduced as a result of this alternative activation. PI3Kδ is one of the mediators involved in determining this alternative phenotype in macrophages and therefore it is proposed that inhibition of PI3Kδ might rebalance macrophage activation towards a classic phagocytic phenotype [Weisser, 2011] facilitating clearance of bacteria, a major cause of exacerbation in COPD. The neutrophil and T cell are the two major inflammatory cell types involved in the pathogenesis of COPD and both are targeted by PI3Kδ inhibitors.

GSK2269557 has demonstrated the ability to protect against and control bacterial infections in preclinical rodent models. This is coupled with recent observations that PI3Kδ inhibition leads to a correction in vitro of aberrant neutrophil chemotaxis directionality in the blood of COPD patients. Furthermore, a human point mutation which results in a constitutively activated version of PI3Kδ has recently been characterised where the majority of affected patients have recurrent lung infections with the same bacterial species which are seen in COPD patients and are known to drive exacerbations. Collectively these data suggest that repeat dosing with GSK2269557 could potentially reduce the impact of an acute exacerbation, or prevent the onset of a secondary bacterial exacerbation or recurrent exacerbation.

Proinflammatory cytokines were reduced by GSK2269557, both in preclinical rodent bacterial models, and COPD patient samples treated in vitro and in the study setting (PII115119).

GSK2269557 has been administered as single and repeat doses to healthy subjects as nebulized solution in the FTIH study PII115117 up to a dose of 6400 µg per day for 7 days. GSK2269557 has also been administered as single and repeat doses to healthy smokers as a dry powder formulation in study PII116617 up to a dose of 3000 µg as single dose and 2000 µg per day for 14 days. GSK2269557 has been well tolerated across the range of doses used. There is also an ongoing study (Study PII115119, non-reported) where a total daily dose of up to 2000 µg of GSK2269557 is being administered to stable COPD patients via a dry powder inhaler for 14 days in a two part study. Part A of this study has completed and Part B will characterise the steady-state (exposure) dose response following repeat inhaled doses of up to 2000µg for the same treatment duration. There is also an on-going larger clinical study PII116678 which is almost identical in design to 201928 using 1000 µg of GSK2269557 per day administered via a Diskus dry powder inhaler to patients diagnosed with an acute exacerbation of COPD. For simplicity study PII116678 does not capture induced sputum hence cannot analyse any changes in mRNA. The primary objective of the current study is to capture induced sputum to enable the mRNA analysis on a smaller cohort.

More information about the non-clinical and clinical studies is available in the GSK2269557 Investigator's Brochure (IB) GlaxoSmithKline Document Number 2012N141231_04.

2.2.1. Use of mRNA transcriptomics by Affymetrix

Analysis of changes in mRNA can be used to demonstrate alterations in biochemical pathways at the gene transcription level. This can be used to better understand the consequences of drug intervention on disease pathophysiology, and ultimately predict alterations which could translate to a positive clinical benefit for patients. Messenger RNA can be extracted from a variety of biological samples (including induced sputum and blood) taken from patients before and after drug dosing to show the impact a drug is having.

The advantage of using Affymetrix is the broad (~50k) gene set covered using this technology enabling great depth in exploring the biological consequences of drug intervention. This technology has been used in previous preclinical and clinical studies using GSK2269557 generating a fingerprint of PI3Kδ inhibition in disease. Importantly these approaches allow areas of complex PI3Kδ-dependent immune cell mechanisms and pathophysiology, specifically related to neutrophil function to be explored which are not easily quantified using other techniques.

2.2.2. Use of HRCT Endpoints to characterise Lung Function

High-resolution computed tomography (HRCT) scans provide a highly detailed insight into the structure and architecture of the respiratory system. A clear distinction can be made between the lung parenchyma, the intraluminal air and alveolar spaces up to the level of the smaller airways with a diameter of 1-2mm. To model dynamic information, low dose HRCT scans can be taken at two lung volumes: after deep inhalation (total lung capacity or TLC) and after normal expiration (functional residual capacity or FRC). The patient's breathing is monitored in real time during the scans to ensure the correct lung levels are scanned. Due to the natural contrast between the intraluminal air and the surrounding tissue, it is possible to attain a significant reduction in radiation dose (1-2 mSv per scan) compared to standard CT protocols (>4 mSv per scan) by reducing the tube current and the voltage. Depending on the patient's weight, a 6- to 10-fold reduction can be obtained per scan without losing image quality. As a comparison, in the USA, the average annual background radiation exposure is 6.2 mSv and a transatlantic flight results in 0.07 mSv exposure.

The high resolution images allow for a three dimensional reconstruction of the airway tree and vasculature by applying segmentation principles. These three dimensional models can be used to measure airway dimensions as well as potentially allowing the phenotyping of patients by disease severity. The three dimensional computer reconstructions can be used for fluid dynamic modelling. This method is used to simulate flow through these airway models and determine the typical flow characteristics such as local pressure drops, velocities and resistance. It can also be used to predict particle deposition in the airways of these patients when using inhaled drug products.

This method consisting of 2 low dose HRCT scans at several time points has previously been used successfully in clinical trials involving COPD patients [De Backer, 2011; De Backer, 2012; De Backer, 2014; Goldin, 1999].

3. OBJECTIVE(S) AND ENDPOINT(S)

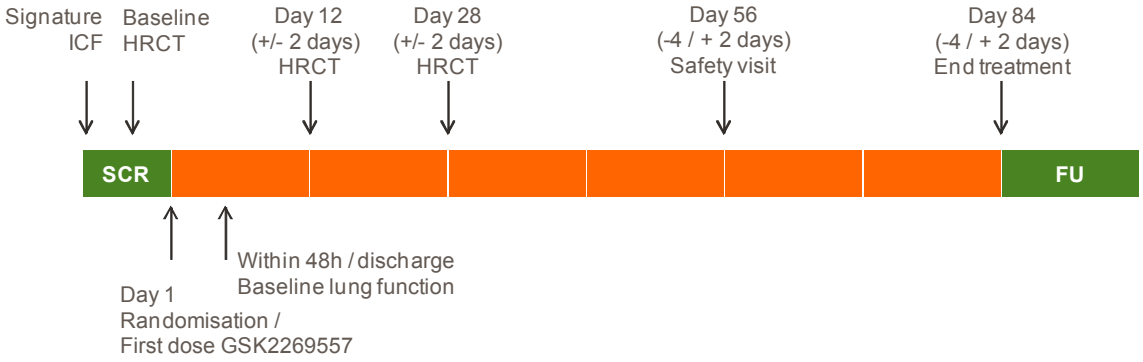
Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Hematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD, compared to placebo	• PEF, Reliever usage. • FEV_1 and FVC at clinic prior to sputum induction.
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.

Objectives	Endpoints
placebo.	
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment.

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual COPD medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



4.2. Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The HRCT scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (±2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table (Section 7.1). Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7 to 14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

4.3. Type and Number of Subjects

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

4.4. Design Justification

This study will include a placebo control to allow for a valid evaluation of the pharmacodynamic endpoints and adverse events attributable to treatment versus those

independent of treatment. Subjects will also receive standard of care for their exacerbation and throughout the study.

4.5. Dose Justification

The dose chosen for this study is 1000 µg of GSK2269557 per day administered via a dry powder inhaler for a duration of 84 days (– 4 / + 2 days). This dose has been selected based on previous safety and tolerability data in man (healthy subjects and COPD subjects) as well as demonstration of target (PI3Kδ) inhibition by observed changes in biomarkers. Together with an additional study to be run in parallel (PII116678), this dose of GSK2269557 is being dosed to subjects in PII116678 with an exacerbation of COPD, so it will be assumed for exposure predictions, unless otherwise stated, that these subjects will have a similar lung deposition, distribution and plasma exposure to that of the healthy volunteers. However it is accepted that these types of subjects may have reduced airway conductance and hence likely reduced deposition. This can be appropriately defined in this study based on the actual plasma exposures achieved.

Twice this dose level (2000 µg) using the same formulation has previously been given once daily to healthy male smokers for 14 days (study PII116617). There is also an ongoing study where a total daily dose of 1000 µg of GSK2269557 is administered to stable COPD subjects via a dry powder inhaler for 14 days (study PII115119) which at the time of writing of this protocol had successfully dosed 21 subjects on active treatment and collected pharmacokinetics (PK) samples for analysis out to 14 days.

The target effect compartment for PI3Kδ inhibition is the intracellular compartment of the immune cells resident in the lung tissue and lumen. GSK2269557 has a high potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL) which translates into an IC_{50} in a more complex system (PHA stimulated lung tissue) of approximately 120 ng/mL (or 2.5 ng/mL free unbound drug). Based on the measured steady-state cellular concentration of GSK2269557 collected at trough (24 h) from the lungs of healthy smokers at 2000 µg DPI (450 ng/mL) in the clinical study it is expected that at 1000 µg (225 ng/mL), concentrations will be sufficient and PI3Kδ inhibition maintained in the lung at ≥ 90% inhibition for 24 h.

Target PI3Kδ inhibition is based on a wide range of pharmacology experiments. Details of these as well as the pharmacokinetics and safety data can be found in the IB, [GlaxoSmithKline Document Number: 2012N141231_04].

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2269557 can be found in the IB [GlaxoSmithKline Document Number 2012N141231_04]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm	A general risk with Inhaled treatment	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Potential photosensitivity	In the absorption spectrum for GSK2269557 there are peaks at the boundary of the ultraviolet (UV) light [UVA/UVB] region with a lambda max at 320 nm (molar extinction coefficient 43800 L/Mol/cm), with smaller peaks at 305 nm and 332 nm.	Subjects will be advised to take UV protection measures (see Section 6.11).
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on screening, Day 12 and Day 28 visits) at are required throughout the study for the functional imaging protocol	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be approximately 12mSv. Final radiation dose will be dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		The outcomes of this study will provide information which would produce advances in knowledge, leading to a potential health benefit in the future for patients in this target population. The CT may also provide information for the patients general clinical management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation.	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the opinion of the Investigator, it is considered safe to do so.

4.6.2. Benefit Assessment

The outcomes of this study will provide information which will produce advances in knowledge of the pathophysiology of COPD exacerbations, leading to a potential health benefit in the future for patients in this target population. The CT scan may also provide information for the patient's general clinical management.

4.6.3. Overall Benefit:Risk Conclusion

The overall benefit:risk is considered to be positive. There is an opportunity to determine if there may be a new drug developable for the treatment of acute exacerbations of COPD which has not seen any new treatments recently. The scientific value in obtaining functional CT information on the anatomy and pathophysiology of COPD exacerbations and how the lung responds to therapy will be extremely valuable to the wider clinical community and justifies the limited radiation exposure (maximum 12 mSv in total) from the CT scan procedures. The CT will also be useful to provide clinical information about the patient for the patient's physician and contribute to clinical management.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number: 2012N141231_04]

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

[1] AGE
• Between 40 and 80 years of age inclusive, at the time of signing the informed consent.
[2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
• The subject has a confirmed and established diagnosis of COPD, as defined by the GOLD guidelines for at least 6 months prior to entry. • The subject is able to produce >100 mg of sputum at screening for processing, (ie, total weight of sputum plugs.). • The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted documented in the last 5 years. • Disease severity: Acute exacerbation of COPD requiring an escalation in therapy to include both corticosteroid and antibiotics. Acute exacerbation to be confirmed by an experienced physician and represent a recent change in at least two major and one minor symptoms, one major and two minor symptoms, or all 3 major symptoms. 1. Major symptoms:

- Subjective increase in dyspnea
- Increase in sputum volume
- Change in sputum colour

2. Minor symptoms:
    - Cough
    - Wheeze
    - Sore throat

- The subject is a smoker or an ex-smoker with a smoking history of at least 10 pack years (pack years = (cigarettes per day smoked/20 x number of years smoked)).

[3] WEIGHT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 16 – 35 kg/m^2 (inclusive).

[4] SEX

- Male
- Female subject : is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

1. Non-reproductive potential defined as:

Pre-menopausal females with one of the following:

Documented tubal ligation

Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion

Hysterectomy

Documented Bilateral Oophorectomy

Postmenopausal defined as 12 months of spontaneous amenorrhea. Females whose menopausal status is in doubt will be required to use, or have been using, one of the highly effective contraception methods as specified below from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

2. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]
3. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
4. Injectable progestogen [Hatcher, 2007a]
5. Contraceptive vaginal ring [Hatcher, 2007a]
6. Percutaneous contraceptive patches [Hatcher, 2007a]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
8. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Specific inclusion criteria for Male subjects with female partners of reproductive potential is outlined below:

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until after the completion of the follow up visit.

3. Vasectomy with documentation of azoospermia.
4. Male condom plus partner use of one of the contraceptive options below:

Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label

Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]

Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a] Contraceptive vaginal ring [Hatcher, 2007a] Percutaneous contraceptive patches [Hatcher, 2007a] 5. These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

[5] INFORMED CONSENT
• Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

• To avoid recruitment of subjects with a severe COPD exacerbation, the presence of any one of the following severity criteria will render the subject ineligible for inclusion in the study:
  • Need for invasive mechanical ventilation (short term (< 48h) NIV or CPAP is acceptable)
  • Haemodynamic instability or clinically significant heart failure
  • Confusion
  • Clinically significant pneumonia, identified by chest X-ray at screening, and as judged by the Investigator.
 	
• Subjects who have current medical conditions or diseases that are not well controlled and, which as judged by the Investigator, may affect subject safety or influence the outcome of the study. (Note: Patients with adequately treated and well controlled concurrent medical conditions (e.g. hypertension or NIDDM) are permitted to be entered into the study).
• Subject has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the subject or affect the interpretation of the results.
• ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if

bilirubin is fractionated and direct bilirubin <35%).

- A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the exclusion criteria, outside of the reference range for the population being studied may be included if the Investigator [in consultation with the GSK Medical Monitor if required] documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
- Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
- ECG indicative of an acute cardiac event (e.g. Myocardial Infarction) or demonstrating a clinically significant arrhythmia requiring treatment.
- QTcF > 450 msec or QTcF > 480 msec in subjects with Bundle Branch Block, based on single QTcF value.
- Subjects who have undergone lung volume reduction surgery.

[2] CONCOMITANT MEDICATIONS

- Subject is currently on chronic treatment with macrolides or long term antibiotics.
- Subject is being treated with long term oxygen therapy - LTOT (> 15 hours/day).
- The subject has been on chronic treatment with anti-Tumour Necrosis Factor (anti-TNF), or any other immunosuppressive therapy (except corticosteroid) within 60 days prior to dosing.

[3] RELEVANT HABITS

- History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >28 units for males or >21 units for 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.

[4] CONTRAINDICATIONS

- History of sensitivity to any of the study medications, or components thereof (such as lactose) or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

[5] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

- A known (historical) positive test for HIV antibody.
- Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.

  NOTE: Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal

Investigator in consultation with the Medical Monitor.

- Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.
- The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
- Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria Protocol Deviations, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of “Lost to Follow-up”.

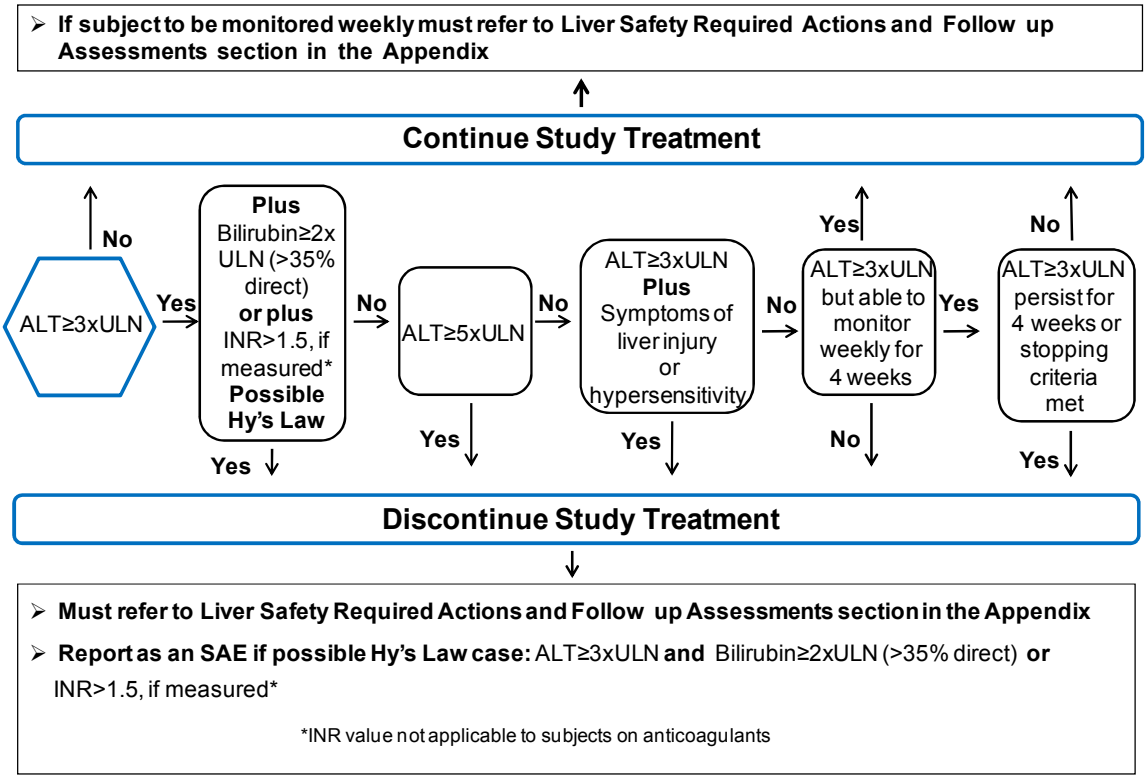
A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn should complete the assessments planned for the follow up visit.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.1.1. Study Treatment Restart or Re-challenge

Study treatment restart or re-challenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.2. QTc Stopping Criteria

- QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. For example, if an ECG (Electrocardiogram) demonstrates a prolonged QTcF interval, obtain two more ECGs and use the averaged QTcF values of the three ECGs to determine whether the patient should be discontinued from the study.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

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

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

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

5.4.3. Other Stopping Safety Criteria

For an individual study participant, stopping criteria include, but are not limited to:

Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests, spirometry assessments, etc), as judged by the Principal Investigator in consultation with the Medical Monitor if necessary.

Treatment failure or recurrent exacerbation does **not** mandate withdrawal from the study, unless there is a safety concern as judged by the Investigator, in consultation with the Medical Monitor if necessary.

Subjects should be withdrawn from the study if confusion, acute respiratory acidosis (pH < 7.30), or need for invasive mechanical ventilation occurs.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment	
Product name:	GSK2269557	Placebo
Formulation description:	Lactose blend containing GSK2269557 in Diskus™ device	Lactose in Diskus device
Dosage form:	Dry powder for inhalation	Dry powder for inhalation
Unit dose strength(s)/Dosage level(s):	500 µg / blister	N/A
Route of Administration	Inhalation	Inhalation
Dosing instructions:	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.

6.2. Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Central based randomisation will be used.

Subjects will be randomised to treatments A or B where:

A = Placebo

B = GSK2269557 1000 µg

A web based interactive response system will be used to assign subjects to treatment.

6.3. Planned Dose Adjustments

If adverse events, unrelated to COPD exacerbation, which are of moderate or severe intensity and are consistent across subjects in the group, or if unacceptable

pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK2269557, are observed in more than 30% of the subjects then the study will be halted and no further subject will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the Ethics Committees will then take place prior to any resumption of dosing. If the above is observed consideration may be given to reducing the dose of GSK2269557 to 500 μg O.D.

6.4. Subject Specific Dose Adjustment Criteria

There are no subject specific dose adjustment criteria.

6.5. Blinding

This will be a double blind study and the following will apply.

- The investigator or treating physician may un-blind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** un-blinding the subject's treatment assignment.
- If GSK personnel are not contacted before the un-blinding, the investigator must notify GSK as soon as possible after un-blinding.
- The date and reason for the un-blinding must be fully documented in the Case Report Form (CRF)
- A subject will be withdrawn if the subject's treatment code is un-blinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the un-blinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may un-blind the treatment assignment for any subject with a Serious Adverse Event (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 subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects 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 labelled 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 (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for 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.

6.8. Compliance with Study Treatment Administration

When subjects 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 subjects will be asked to complete a diary when dose administration takes place at home. The date, time and number of inhalations will be recorded. The compliance will be checked by the site staff at each planned visit.

A record of the number of Diskus inhalers dispensed to each subject and the number of actuation administered, read from the dose counter for each Diskus inhaler, must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.9. Treatment of Study Treatment Overdose

For this study, any dose of GSK2269557 >2000 µg within a 22 hour time period will be considered an overdose.

GSK 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 subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2269557 can no longer be detected systemically (at least 14 days for GSK2269557)
3) obtain a plasma sample for pharmacokinetic (PK) analysis within 7 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 subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Any clinical abnormalities identified during the conduct of the study will be locally managed by the Investigator.

6.11. Lifestyle and/or Dietary Restrictions

- Subjects must not sunbathe or use a tanning device (e.g. sunbed or solarium) whilst taking the study medication and until at least 2 weeks after their last dose. Subjects are to be advised that they should cover exposed areas of skin (e.g. use sun hat, long sleeves) and use a broad spectrum UVA/UVB sunscreen (SPF ≥30) on exposed areas of skin when outdoors.
- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.

- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit, and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

6.12.2. Prohibited Medications and Non-Drug Therapies

Regular or chronic treatment with medications that are considered strong inhibitors of CYP3A4 or CYP2D6 are not permitted. This includes anti-epileptic treatments, macrolide antibiotics, oral antifungal treatments (single doses and courses up to 7 days are allowed) and anti-tuberculous therapy. These medications must all have been stopped at least 14 days prior to first dose.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table (Screening and Follow Up Visits)

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Informed consent	X		
Demography	X		
Inclusion and exclusion criteria	X		
Full physical exam, including height and weight	X		
Brief physical examination, including weight		X	
Chest X-Ray	X		To be done before baseline HRCT to exclude significant pneumonia and other incidental serious underlying pathology.
Medical history (includes substance usage and Family history of premature CV disease)	X		Substances: Drugs, Alcohol, tobacco via history. No drug, alcohol screening is required.
Past and current medical conditions (including cardiovascular medical history and therapy history)	X		
Laboratory assessments (include Hematology and biochemistry)[1]	X	X	Historical values analysed by local lab to be used for eligibility assessment. Another sample must be collected and sent to central lab as soon as informed consent is obtained.
Hep B and Hep C screen[2]	X		
Urine pregnancy test (only WCBP)	X		Before conducting the HRCT. Done locally at the site.
12-lead ECG	X	X	Single assessment
Vital signs	X	X	Single assessment
HRCT (at TLC and FRC)	X		Within 48 h of diagnosis, if subject otherwise eligible. Includes electronic monitoring of breathing (if applicable). Baseline HRCT will be reviewed by the local site's radiologist to identify any significant occurring underlying medical conditions that require further clinical management or monitoring.
Induced Sputum[3]	X[4]		To include sputum culture pre-first dose. Culture to be done by the local site laboratory.

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Blood sample for mRNA Analysis	X[4]		Collected at any time on specified days
AE/SAE collection and review		X	
Concomitant medication review	X	X	

1. Due to the short screening window, central laboratory analysis results will not be available on time. Therefore the local laboratory results should be used for eligibility assessment (to exclude severe subjects and underlying medical conditions). If local laboratory results are already available from diagnosis of current exacerbation, there is no need to take another sample for local analysis. A sample for central laboratory analysis should also be obtained. See Section 7.8.6 for further details.
2. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required. Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor.

3. Induced sputum collection may be attempted on several occasions if an adequate sample is not produced at the first attempt.
4. To be collected at any time point before randomisation.

7.2. Time and Events Table (Treatment Period)

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========					==========→	Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

1. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
2. Assessments do not need to be completed if screening assessments conducted within 48 hours
3. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
4. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

7.3. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

If they are being utilised in the study, Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

7.4. Biomarker(s)/Pharmacodynamic Markers

7.4.1. Pharmacodynamic Biomarkers in Sputum

- Collect sputum induction samples at the time-points shown in the time and events table (Section 7.1).
- The sputum induction collection process will follow local standard procedures and guidelines outlined in the SRM.
- The collection of induced sputum may be attempted on several occasions if an adequate sample is not produced at the first attempt.
- Further information on collection, processing, storage and shipping procedures are provided in the SRM.

7.4.2. mRNA in blood

- Collect 2.5 mL of blood into a PAXgene mRNA tube.

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

7.5. Patient diary

The subjects will be provided with a diary to record the following data when at home:

- Time and date of each dose administration and number of inhalations.

- Adverse Events and concomitant medications taken (including daily rescue medication – if used and how many times used).
- PEF from a handheld device. The best/highest result is recorded.

Changes in Health and details of any concomitant medications as well as PEF assessment details will be collected in the paper diaries and later transcribed into the CRF.

7.6. Genetics

Information regarding genetic research is included in Appendix 3.

7.7. Efficacy

7.7.1. Functional Respiratory Imaging

- A CT scan with a low radiation protocol at FRC and TLC will be conducted as listed in the Time and Events Table (Section 7.1). The same scanner should be used for baseline and post-treatment scans for an individual subject.
- A urine pregnancy test should be performed before the CT scan in female subjects of childbearing potential.
- Further information is provided in the SRM.

7.7.2. FEV_1 and FVC

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. These will be recorded as absolute values. The best/highest result is recorded.

- Further details are provided in the SRM.

7.7.3. Peak Expiratory Flow PEF

- PEF measurements will be taken (in triplicate) daily in the morning before dose administration, as soon as it is safe for the subject to do so. The best/highest result is recorded.
- Subjects will be provided with a handheld device.
- Further details are provided in the SRM.

7.8. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.8.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.8.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.8.1.3), at the time-points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.8.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.8.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

7.8.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

7.8.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless they meet the definition of an SAE as defined in Appendix 4 Exacerbations that meet the definition of an SAE will be recorded on the appropriate eCRF section and should be reported to GSK.

Medications used to treat a COPD exacerbation will be recorded in the exacerbation eCRF

7.8.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.8.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until the follow-up visit
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.8.3. Physical Exams

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

7.8.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.
- Three readings of blood pressure and pulse rate will be taken
- First reading should be rejected
- Second and third readings should be averaged to give the measurement to be recorded in the CRF.

7.8.5. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at screening and at each other timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

7.8.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Historical values (if the assessment was conducted as part of the standard of care) for blood gases, blood culture and sputum culture may also be collected if available.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Table 1 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential:</u></td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose (non fasted)</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
<tr><td>CRP</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>• Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)</td></tr>
</table>

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 5.4.1 and Appendix 2
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Hematology and clinical chemistry at screening for excluding subjects with severe disease and uncontrolled medical conditions. The results of each test must be entered into the CRF.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Hematology, clinical chemistry and additional parameters to be tested are listed in Table 1.

7.9. Pharmacokinetics

7.9.1. Blood Sample Collection

A 2 mL blood samples for pharmacokinetic (PK) analysis of GSK2269557 will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.9.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK2269557 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for GSK2269557 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK/Scinovo, GlaxoSmithKline protocol.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

This study is designed to establish the PI3Kδ-dependent alterations in immune cell mechanisms related to neutrophil function as detected by changes in mRNA transcriptomics in samples of induced sputum from patients admitted with an exacerbation of COPD. The primary comparison will be between subjects treated with GSK2269557 in addition to standard of care, and subjects treated with placebo in addition to standard of care. In addition, treatment comparisons between subjects at baseline and subsequent time points will also be produced.

9.1. Sample Size Considerations

The sample size for this study has been based on feasibility. The sample size of 30 subjects completing the trial, with approximately 15 of which will receive GSK2269557 and 15 will receive placebo, is expected to be sufficient to provide a meaningful estimate of the mRNA alterations within the lungs.

Previous studies with similar sample size populations have yielded significant fold-changes (fold-change>1.5 and $p<0.05$) in immune cell mechanisms using the changes in mRNA transcriptomics.

Study Name	Sample	Study Design	Number of Subjects	Number of Differential probesets FC = >= 1.5, Pval <= 0.05	Notes
PII115117 FTIH Healthy Smoker nebulised GSK2269557	Sputum	Sputum N=12 3-way x-over placebo 400ug, 6400ug	12 (9 with all data points)	57 probesets change with both doses = 44 Genes	Gene changes relate predominantly to a down regulation of infection and inflammation responses. Link to Haemophilus influenzae and Moraxella catarrhalis infection biology – Identified prior to knowledge of Activated PI3Kδ Syndrome phenotype
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Sputum	Ex vivo Sputum incubated with GSK2269557 sampled at 6hrs (Sputum producers)	15 Subjects	490 probesets change vs vehicle control = 295 genes (of which 43 are dysregulated in COPD disease vs Healthy comparison)	43 genes altered in COPD and positively modulated by PI3Kδi GSK2269557. Biological themes in signature: Pro-cell movement/migration and cell viability, anti-apoptotic. Additionally link to B/T cell function. Signature supports GSK2269557 correction of neutrophil migration
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at 6hrs (Sputum	15 Subjects	19 probesets change vs vehicle control = 15 genes	Infection and inflammation associated genes
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at	15 Subjects	30 probesets change vs vehicle control = 25 genes	Infection and inflammation associated genes

9.1.1. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed in this study.

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Screened	• All subjects who were screened.	• Study Population
All subject	• All randomised subjects who receive at least one dose of the study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Pharmacodynamics • Safety • Efficacy
Pharmacokinetic	• Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.	• PK

9.2.2. Interim Analysis

No interim analyses will be performed.

9.3. Key Elements of Analysis Plan

9.3.1. Primary Analyses

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

Further details around the analysis of the mRNA data will be provided in the RAP.

9.3.2. Secondary Analyses

All secondary analyses will be described in full prior to unblinding in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable

- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the

regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
ECG	Electrocardiogram
FEV1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
GCP	ICH Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
PEF	Peak Expiratory Flow
PI3Kδ	Phosphoinositide 3-Kinase Delta
PK	Pharmacokinetic
QTcF	QT interval corrected using the Fridericia's formula
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SRM	Study Reference Manual
TLC	Total Lung Capacity
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DISKUS

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **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 subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (refer to Appendix 2).	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained 7 days after last dose[5] • 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

• If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments	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
MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**<u>For bilirubin or INR criteria:</u>** • 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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, 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 subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

4. 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
5. PK sample may not be required for subjects 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 blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.3. Appendix 3: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- COPD susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to

the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.

- Situations where 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.

12.4.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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 disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are 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

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject'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 instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject 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 the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication

Pregnancy information on female partner of male study subjects

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks 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: Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7: Protocol Amendment Changes

Protocol Amendment #1 Changes

The amendment was created to remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria (European Community of Coal and Steel and European Respiratory Society Global Lung Function Initiative reference equations (Quanjer 2012) in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. As a result it may not be valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.

List of specific changes:

Page 22, Inclusion Criteria (#2 – Type of Subject and Diagnosis Including Disease Severity) - Third Bullet.

PREVIOUS TEXT

- The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted. Predictions should be according to the European Community of Coal and Steel (ECCS) equations OR the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012] and documented in the last 5 years.

REVISED TEXT

- The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted documented in the last 5 years.

Page 40, Section 7.7.2 (FEV_1 and FVC)

PREVIOUS TEXT

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. Predicted values will be based upon the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012].

REVISED TEXT

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. These will be recorded as absolute values. The best/highest result is recorded.

Page 54 – References

PREVIOUS TEXT

De Backer J, Vos W, Vinchurkar S, Van Holsbeke C, Poli, G, Claes R et al. The Effect of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Fundtional Respiratory Imaging. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:1-12.

De Backer LA, Vos WG, Salgado R, De Backer JW, Devoldr A, Verhulst SL et al. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD. *International Journal of COPD.* 2011;6:637-646.

De Backer Lieve A, Vos Wim, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. *Eur Respir J.* 2012;40:298-305.

GlaxoSmithKline Document Number 2012N141231_04: GSK2269557 Investigator's Brochure. Report Date 12-FEB-2015.

Goldin J, Tashkin D, Kleerup E, Greaser MS, Haywood U, Sayre J et al. Comparative effects of hydrofluoroalkane and chloroflurocarbon beclomethasone dipropionate inhalation on small airways: Assessment with functional helical thin-section computed tomography. *J Allergy Clin Immunol.* 1999;104 #6:S258-S267.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(a):24. Table 3-2.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(b): 28.

ICRP. 2007 Recommendation of the International Commission on Radiological Protection. *ICRP Publication 103.* 2007;37:2-4.

Kim SR, Lee KS, Park HS, et al. HIF -1 alpha inhibition ameliorates an allergic airway disease via VEGF suppression in bronchial epithelium. *Eur J Immunol.* 2010;40 (10):2858-69.

Okkenhaug K, Aki K, Vanhaesebroeck B. Antigen receptor signalling: A distincive role for the p110 isoform of PI3K. *Trends in Immunuology.* 2007;28:80-7.

Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *European Respiratory Journal.* 2012;40(6):1324-1343.

Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI13K delta in neutrophil inflammatory responses. *Biochem Biophys Res Commun.* 2003 Sep 5;308 (4):764-9.

Weisser SB, McLarren KW, Voglmaier B, et al. Alternative activation of macrophages by IL-4 requires SHIP degradation. *Eur J Immunol.* 2011;41(6):1742-53.

REVISED TEXT

De Backer J, Vos W, Vinchurkar S, Van Holsbeke C, Poli, G, Claes R et al. The Effect of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Fundtional Respiratory Imaging. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:1-12.

De Backer LA, Vos WG, Salgado R, De Backer JW, Devoldr A, Verhulst SL et al. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD. *International Journal of COPD.* 2011;6:637-646.

De Backer Lieve A, Vos Wim, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. *Eur Respir J.* 2012;40:298-305.

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Okkenhaug K, Aki K, Vanhaesebroeck B. Antigen receptor signalling: A distincive role for the p110 isoform of PI3K. *Trends in Immunuology.* 2007;28:80-7.

Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI13K delta in neutrophil inflammatory responses. *Biochem Biophys Res Commun.* 2003 Sep 5;308 (4):764-9.

Weisser SB, McLarren KW, Voglmaier B, et al. Alternative activation of macrophages by IL-4 requires SHIP degradation. *Eur J Immunol.* 2011;41(6):1742-53.

Protocol Amendment #2 Changes

This amendment was created to widen the Body Mass Index (BMI) range at the screening visit as the propose range from 16 – 35 kg/m^2 would be appropriate for the COPD subject population.

List of specific changes:

Page 22, Inclusion Criteria (#3 – Weight).

PREVIOUS TEXT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 18 – 32 kg/m^2 (inclusive).

REVISED TEXT

- Body weight ≥ 45 kg and body mass index (BMI) within the range 16 – 35 kg/m^2 (inclusive).

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).

Compound Number: GSK2269557

Development Phase: IIA

Effective Date: 30-NOV-2015

Protocol Amendment Number: 01

Author (s): PPD (CCSE); PPD (CPSSO); PPD (Respiratory CEDD); PPD (Exp Biology); PPD (Clinical Statistics); PPD (CPMS); PPD (GCSP).

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2014N218070_00	2015-JUN-04	Original
2014N218070_01	2015-NOV-30	Amendment No. 1

Remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria and in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. It therefore is not valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.

SPONSOR SIGNATORY

(P.P) PPD

HEAD OF RESPIRATORY DISCOVERY MEDICINE

30-NOV-2015

Steven Pascoe
VP TA Clinical Development Leader

Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
Secondary Medical Monitor					Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

PROTOCOL AGREEMENT PAGE

For protocol 201928:

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

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1. PROTOCOL SYNOPSIS FOR STUDY 201928

Rationale

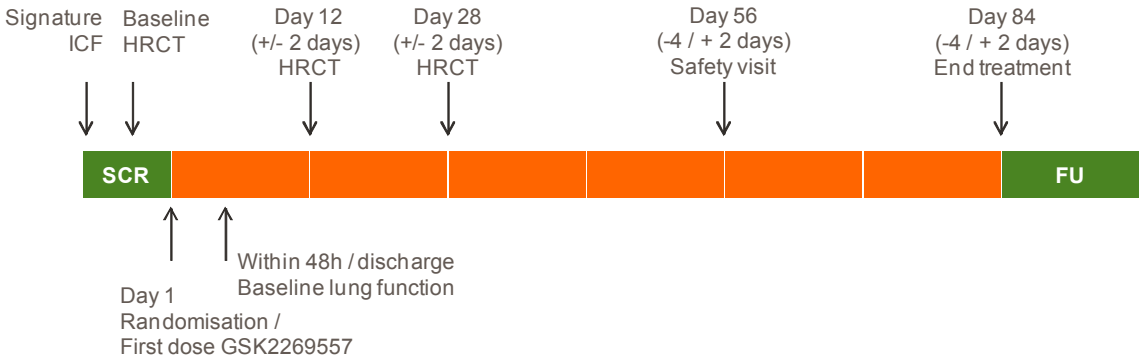
Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Haematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD.	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.	• PEF • Reliever usage • $FEV_{1\ and}$ FVC at clinic prior to sputum induction
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral

Objectives	Endpoints
administered to subjects with acute exacerbation of COPD, compared to placebo.	qPCR.
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment

Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual Chronic Obstructive Pulmonary Disease (COPD) medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The High-Resolution Computed Tomography (HRCT) scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (± 2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table. Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7-14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

Type and Number of Subjects

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected numbers of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

Analysis

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

2. INTRODUCTION

GSK2269557 is a potent and highly selective inhaled Phosphoinositide 3-Kinase Delta (PI3Kδ) inhibitor being developed as an anti-inflammatory and anti-infective agent for the treatment of inflammatory airways diseases.

2.1. Study Rationale

The purpose of this study is to evaluate specific alterations in immune cell mechanisms related to neutrophil function as detected by PI3Kδ-dependent changes in mRNA extracted from induced sputum in patients experiencing an exacerbation of COPD. In addition this study will also further evaluate the plasma PK and assess the safety of GSK2269557 administered to patients diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD). The efficacy of treatment with GSK2269557 will also be measured using functional respiratory imaging (FRI) and spirometry.

This study will also explore the pharmacodynamic effects of once daily repeat doses of inhaled GSK2269557 on cytokines, mediators and microbiome in induced sputum samples. These will be obtained from subjects at entry, during their exacerbation, and at additional time points over the 12 week treatment period. To understand patient efficacy, at entry, Day 12 and Day28 the sputum biomarker data will be correlated with computed tomography (CT).

2.2. Brief Background

PI3Kδ is a member of the Class IA family of phosphoinositides 3-kinases (PI3Ks) that convert the membrane phospholipid phosphatidylinositol 4,5-biphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is a second messenger in many cellular processes including cell growth, differentiation and migration. PI3Kδ has specific roles in mediating antigen receptor and cytokine signalling in T-cells, mast cells and B-cells [Okkenhaug, 2007] and roles in neutrophil chemotaxis and activation [Sadhu, 2003]. A PI3Kδ inhibitor has the potential to inhibit major cell types responsible for the inflammation associated with both COPD and asthma.

In COPD, tobacco smoke or other irritants activate epithelial cells and macrophages to release inflammatory mediators such as chemokines that attract neutrophils and T cells to the lungs. PI3Kδ is thought to play a role in a number of epithelial responses relevant for the development of COPD. Therefore a PI3Kδ inhibitor may be able to suppress a number of these processes [Kim, 2010]. A greater proportion of macrophages appear to be alternatively activated in COPD and their ability to phagocytose infective pathogens is reduced as a result of this alternative activation. PI3Kδ is one of the mediators involved in determining this alternative phenotype in macrophages and therefore it is proposed that inhibition of PI3Kδ might rebalance macrophage activation towards a classic phagocytic phenotype [Weisser, 2011] facilitating clearance of bacteria, a major cause of exacerbation in COPD. The neutrophil and T cell are the two major inflammatory cell types involved in the pathogenesis of COPD and both are targeted by PI3Kδ inhibitors.

GSK2269557 has demonstrated the ability to protect against and control bacterial infections in preclinical rodent models. This is coupled with recent observations that PI3Kδ inhibition leads to a correction in vitro of aberrant neutrophil chemotaxis directionality in the blood of COPD patients. Furthermore, a human point mutation which results in a constitutively activated version of PI3Kδ has recently been characterised where the majority of affected patients have recurrent lung infections with the same bacterial species which are seen in COPD patients and are known to drive exacerbations. Collectively these data suggest that repeat dosing with GSK2269557 could potentially reduce the impact of an acute exacerbation, or prevent the onset of a secondary bacterial exacerbation or recurrent exacerbation.

Proinflammatory cytokines were reduced by GSK2269557, both in preclinical rodent bacterial models, and COPD patient samples treated in vitro and in the study setting (PII115119).

GSK2269557 has been administered as single and repeat doses to healthy subjects as nebulized solution in the FTIH study PII115117 up to a dose of 6400 µg per day for 7 days. GSK2269557 has also been administered as single and repeat doses to healthy smokers as a dry powder formulation in study PII116617 up to a dose of 3000 µg as single dose and 2000 µg per day for 14 days. GSK2269557 has been well tolerated across the range of doses used. There is also an ongoing study (Study PII115119, non-reported) where a total daily dose of up to 2000 µg of GSK2269557 is being administered to stable COPD patients via a dry powder inhaler for 14 days in a two part study. Part A of this study has completed and Part B will characterise the steady-state (exposure) dose response following repeat inhaled doses of up to 2000µg for the same treatment duration. There is also an on-going larger clinical study PII116678 which is almost identical in design to 201928 using 1000 µg of GSK2269557 per day administered via a Diskus dry powder inhaler to patients diagnosed with an acute exacerbation of COPD. For simplicity study PII116678 does not capture induced sputum hence cannot analyse any changes in mRNA. The primary objective of the current study is to capture induced sputum to enable the mRNA analysis on a smaller cohort.

More information about the non-clinical and clinical studies is available in the GSK2269557 Investigator's Brochure (IB) GlaxoSmithKline Document Number 2012N141231_04.

2.2.1. Use of mRNA transcriptomics by Affymetrix

Analysis of changes in mRNA can be used to demonstrate alterations in biochemical pathways at the gene transcription level. This can be used to better understand the consequences of drug intervention on disease pathophysiology, and ultimately predict alterations which could translate to a positive clinical benefit for patients. Messenger RNA can be extracted from a variety of biological samples (including induced sputum and blood) taken from patients before and after drug dosing to show the impact a drug is having.

The advantage of using Affymetrix is the broad (~50k) gene set covered using this technology enabling great depth in exploring the biological consequences of drug intervention. This technology has been used in previous preclinical and clinical studies using GSK2269557 generating a fingerprint of PI3Kδ inhibition in disease. Importantly these approaches allow areas of complex PI3Kδ-dependent immune cell mechanisms and pathophysiology, specifically related to neutrophil function to be explored which are not easily quantified using other techniques.

2.2.2. Use of HRCT Endpoints to characterise Lung Function

High-resolution computed tomography (HRCT) scans provide a highly detailed insight into the structure and architecture of the respiratory system. A clear distinction can be made between the lung parenchyma, the intraluminal air and alveolar spaces up to the level of the smaller airways with a diameter of 1-2mm. To model dynamic information, low dose HRCT scans can be taken at two lung volumes: after deep inhalation (total lung capacity or TLC) and after normal expiration (functional residual capacity or FRC). The patient's breathing is monitored in real time during the scans to ensure the correct lung levels are scanned. Due to the natural contrast between the intraluminal air and the surrounding tissue, it is possible to attain a significant reduction in radiation dose (1-2 mSv per scan) compared to standard CT protocols (>4 mSv per scan) by reducing the tube current and the voltage. Depending on the patient's weight, a 6- to 10-fold reduction can be obtained per scan without losing image quality. As a comparison, in the USA, the average annual background radiation exposure is 6.2 mSv and a transatlantic flight results in 0.07 mSv exposure.

The high resolution images allow for a three dimensional reconstruction of the airway tree and vasculature by applying segmentation principles. These three dimensional models can be used to measure airway dimensions as well as potentially allowing the phenotyping of patients by disease severity. The three dimensional computer reconstructions can be used for fluid dynamic modelling. This method is used to simulate flow through these airway models and determine the typical flow characteristics such as local pressure drops, velocities and resistance. It can also be used to predict particle deposition in the airways of these patients when using inhaled drug products.

This method consisting of 2 low dose HRCT scans at several time points has previously been used successfully in clinical trials involving COPD patients [De Backer, 2011; De Backer, 2012; De Backer, 2014; Goldin, 1999].

3. OBJECTIVE(S) AND ENDPOINT(S)

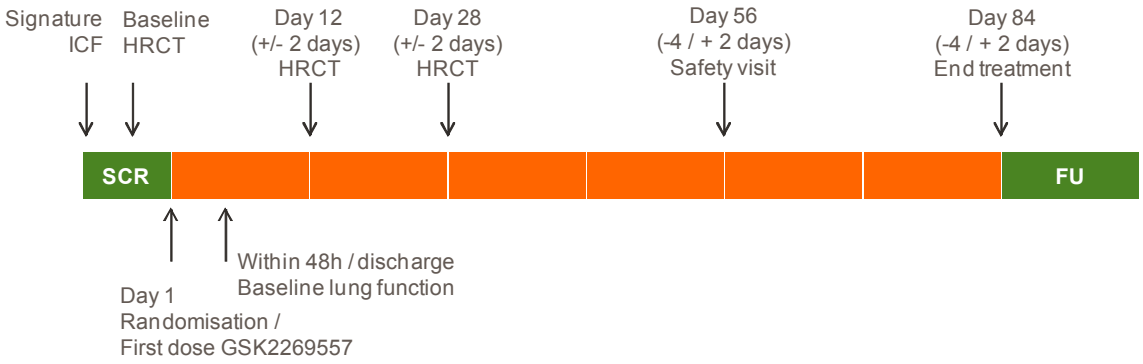
Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Hematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD, compared to placebo	• PEF, Reliever usage. • FEV_1 and FVC at clinic prior to sputum induction.
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.

Objectives	Endpoints
placebo.	
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment.

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual COPD medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



4.2. Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The HRCT scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (±2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table (Section 7.1). Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7 to 14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

4.3. Type and Number of Subjects

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

4.4. Design Justification

This study will include a placebo control to allow for a valid evaluation of the pharmacodynamic endpoints and adverse events attributable to treatment versus those

independent of treatment. Subjects will also receive standard of care for their exacerbation and throughout the study.

4.5. Dose Justification

The dose chosen for this study is 1000 µg of GSK2269557 per day administered via a dry powder inhaler for a duration of 84 days (– 4 / + 2 days). This dose has been selected based on previous safety and tolerability data in man (healthy subjects and COPD subjects) as well as demonstration of target (PI3Kδ) inhibition by observed changes in biomarkers. Together with an additional study to be run in parallel (PII116678), this dose of GSK2269557 is being dosed to subjects in PII116678 with an exacerbation of COPD, so it will be assumed for exposure predictions, unless otherwise stated, that these subjects will have a similar lung deposition, distribution and plasma exposure to that of the healthy volunteers. However it is accepted that these types of subjects may have reduced airway conductance and hence likely reduced deposition. This can be appropriately defined in this study based on the actual plasma exposures achieved.

Twice this dose level (2000 µg) using the same formulation has previously been given once daily to healthy male smokers for 14 days (study PII116617). There is also an ongoing study where a total daily dose of 1000 µg of GSK2269557 is administered to stable COPD subjects via a dry powder inhaler for 14 days (study PII115119) which at the time of writing of this protocol had successfully dosed 21 subjects on active treatment and collected pharmacokinetics (PK) samples for analysis out to 14 days.

The target effect compartment for PI3Kδ inhibition is the intracellular compartment of the immune cells resident in the lung tissue and lumen. GSK2269557 has a high potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL) which translates into an IC_{50} in a more complex system (PHA stimulated lung tissue) of approximately 120 ng/mL (or 2.5 ng/mL free unbound drug). Based on the measured steady-state cellular concentration of GSK2269557 collected at trough (24 h) from the lungs of healthy smokers at 2000 µg DPI (450 ng/mL) in the clinical study it is expected that at 1000 µg (225 ng/mL), concentrations will be sufficient and PI3Kδ inhibition maintained in the lung at ≥ 90% inhibition for 24 h.

Target PI3Kδ inhibition is based on a wide range of pharmacology experiments. Details of these as well as the pharmacokinetics and safety data can be found in the IB, [GlaxoSmithKline Document Number: 2012N141231_04].

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2269557 can be found in the IB [GlaxoSmithKline Document Number 2012N141231_04]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm	A general risk with Inhaled treatment	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital.
Mucosal irritancy	Detected in 13 week toxicology study in the dog	Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Potential photosensitivity	In the absorption spectrum for GSK2269557 there are peaks at the boundary of the ultraviolet (UV) light [UVA/UVB] region with a lambda max at 320 nm (molar extinction coefficient 43800 L/Mol/cm), with smaller peaks at 305 nm and 332 nm.	Subjects will be advised to take UV protection measures (see Section 6.11).
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on screening, Day 12 and Day 28 visits) at are required throughout the study for the functional imaging protocol	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be approximately 12mSv. Final radiation dose will be dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		The outcomes of this study will provide information which would produce advances in knowledge, leading to a potential health benefit in the future for patients in this target population. The CT may also provide information for the patients general clinical management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation..	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the opinion of the Investigator, it is considered safe to do so.

4.6.2. Benefit Assessment

The outcomes of this study will provide information which will produce advances in knowledge of the pathophysiology of COPD exacerbations, leading to a potential health benefit in the future for patients in this target population. The CT scan may also provide information for the patient's general clinical management.

4.6.3. Overall Benefit:Risk Conclusion

The overall benefit:risk is considered to be positive. There is an opportunity to determine if there may be a new drug developable for the treatment of acute exacerbations of COPD which has not seen any new treatments recently. The scientific value in obtaining functional CT information on the anatomy and pathophysiology of COPD exacerbations and how the lung responds to therapy will be extremely valuable to the wider clinical community and justifies the limited radiation exposure (maximum 12 mSv in total) from the CT scan procedures. The CT will also be useful to provide clinical information about the patient for the patient's physician and contribute to clinical management.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number: 2012N141231_04]

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

[1] AGE
• Between 40 and 80 years of age inclusive, at the time of signing the informed consent.
[2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
• The subject has a confirmed and established diagnosis of COPD, as defined by the GOLD guidelines for at least 6 months prior to entry. • The subject is able to produce >100 mg of sputum at screening for processing, (ie, total weight of sputum plugs.). • The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted documented in the last 5 years. • Disease severity: Acute exacerbation of COPD requiring an escalation in therapy to include both corticosteroid and antibiotics. Acute exacerbation to be confirmed by an experienced physician and represent a recent change in at least two major and one minor symptoms, one major and two minor symptoms, or all 3 major symptoms.

1. Major symptoms:
    - Subjective increase in dyspnea
    - Increase in sputum volume
    - Change in sputum colour
2. Minor symptoms:
    - Cough
    - Wheeze
    - Sore throat

- The subject is a smoker or an ex-smoker with a smoking history of at least 10 pack years (pack years = (cigarettes per day smoked/20 x number of years smoked)).

[3] WEIGHT
• Body weight ≥ 45 kg and body mass index (BMI) within the range 18 – 32 kg/m^2 (inclusive).
[4] SEX
• Male • Female subject : is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies: 1. Non-reproductive potential defined as: Pre-menopausal females with one of the following: Documented tubal ligation Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion Hysterectomy Documented Bilateral Oophorectomy Postmenopausal defined as 12 months of spontaneous amenorrhea. Females whose menopausal status is in doubt will be required to use, or have been using, one of the highly effective contraception methods as specified below from 30 days prior to the first dose of study medication and until completion of the follow-up visit. 2. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]
3. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
4. Injectable progestogen [Hatcher, 2007a]
5. Contraceptive vaginal ring [Hatcher, 2007a]
6. Percutaneous contraceptive patches [Hatcher, 2007a]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
8. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Specific inclusion criteria for Male subjects with female partners of reproductive potential is outlined below:

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until after the completion of the follow up visit.

3. Vasectomy with documentation of azoospermia.
4. Male condom plus partner use of one of the contraceptive options below:

Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label

Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]

Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a] Contraceptive vaginal ring [Hatcher, 2007a] Percutaneous contraceptive patches [Hatcher, 2007a] 5. These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

[5] INFORMED CONSENT
• Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

• To avoid recruitment of subjects with a severe COPD exacerbation, the presence of any one of the following severity criteria will render the subject ineligible for inclusion in the study:
  • Need for invasive mechanical ventilation (short term (< 48h) NIV or CPAP is acceptable)
  • Haemodynamic instability or clinically significant heart failure
  • Confusion
  • Clinically significant pneumonia, identified by chest X-ray at screening, and as judged by the Investigator.
 	
• Subjects who have current medical conditions or diseases that are not well controlled and, which as judged by the Investigator, may affect subject safety or influence the outcome of the study. (Note: Patients with adequately treated and well controlled concurrent medical conditions (e.g. hypertension or NIDDM) are permitted to be entered into the study).
• Subject has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the subject or affect the interpretation of the results.
• ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if

bilirubin is fractionated and direct bilirubin <35%).

- A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the exclusion criteria, outside of the reference range for the population being studied may be included if the Investigator [in consultation with the GSK Medical Monitor if required] documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
- Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
- ECG indicative of an acute cardiac event (e.g. Myocardial Infarction) or demonstrating a clinically significant arrhythmia requiring treatment.
- QTcF > 450 msec or QTcF > 480 msec in subjects with Bundle Branch Block, based on single QTcF value.
- Subjects who have undergone lung volume reduction surgery.

[2] CONCOMITANT MEDICATIONS

- Subject is currently on chronic treatment with macrolides or long term antibiotics.
- Subject is being treated with long term oxygen therapy - LTOT (> 15 hours/day).
- The subject has been on chronic treatment with anti-Tumour Necrosis Factor (anti-TNF), or any other immunosuppressive therapy (except corticosteroid) within 60 days prior to dosing.

[3] RELEVANT HABITS

- History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >28 units for males or >21 units for 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.

[4] CONTRAINDICATIONS

- History of sensitivity to any of the study medications, or components thereof (such as lactose) or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

[5] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

- A known (historical) positive test for HIV antibody.
- Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.

  NOTE: Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal

Investigator in consultation with the Medical Monitor.

- Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days.
- The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
- Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria Protocol Deviations, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of “Lost to Follow-up”.

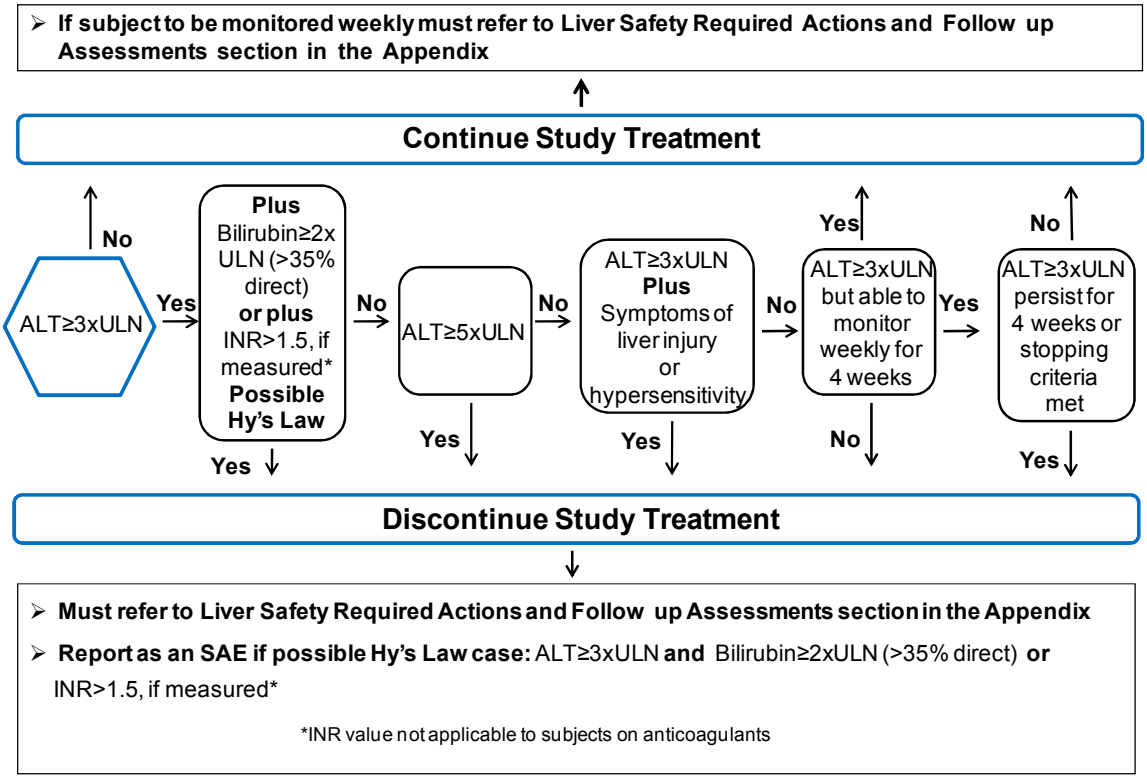
A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Subjects who are withdrawn should complete the assessments planned for the follow up visit.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.1.1. Study Treatment Restart or Re-challenge

Study treatment restart or re-challenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.2. QTc Stopping Criteria

- QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. For example, if an ECG (Electrocardiogram) demonstrates a prolonged QTcF interval, obtain two more ECGs and use the averaged QTcF values of the three ECGs to determine whether the patient should be discontinued from the study.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

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

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

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

5.4.3. Other Stopping Safety Criteria

For an individual study participant, stopping criteria include, but are not limited to:

Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests, spirometry assessments, etc), as judged by the Principal Investigator in consultation with the Medical Monitor if necessary.

Treatment failure or recurrent exacerbation does **not** mandate withdrawal from the study, unless there is a safety concern as judged by the Investigator, in consultation with the Medical Monitor if necessary.

Subjects should be withdrawn from the study if confusion, acute respiratory acidosis (pH < 7.30), or need for invasive mechanical ventilation occurs.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment	
Product name:	GSK2269557	Placebo
Formulation description:	Lactose blend containing GSK2269557 in Diskus™ device	Lactose in Diskus device
Dosage form:	Dry powder for inhalation	Dry powder for inhalation
Unit dose strength(s)/Dosage level(s):	500 µg / blister	N/A
Route of Administration	Inhalation	Inhalation
Dosing instructions:	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.

6.2. Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Central based randomisation will be used.

Subjects will be randomised to treatments A or B where:

A = Placebo

B = GSK2269557 1000 µg

A web based interactive response system will be used to assign subjects to treatment.

6.3. Planned Dose Adjustments

If adverse events, unrelated to COPD exacerbation, which are of moderate or severe intensity and are consistent across subjects in the group, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK2269557, are observed in more than 30% of the subjects then the study will be halted and no further subject will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the Ethics Committees will then take place prior to any resumption of dosing. If the above is observed consideration may be given to reducing the dose of GSK2269557 to 500 µg O.D.

6.4. Subject Specific Dose Adjustment Criteria

There are no subject specific dose adjustment criteria.

6.5. Blinding

This will be a double blind study and the following will apply.

- The investigator or treating physician may un-blind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** un-blinding the subject's treatment assignment.
- If GSK personnel are not contacted before the un-blinding, the investigator must notify GSK as soon as possible after un-blinding.
- The date and reason for the un-blinding must be fully documented in the Case Report Form (CRF)
- A subject will be withdrawn if the subject's treatment code is un-blinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the un-blinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may un-blind the treatment assignment for any subject with a Serious Adverse Event (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 subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects 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 labelled 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 (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for 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.

6.8. Compliance with Study Treatment Administration

When subjects 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 subjects will be asked to complete a diary when dose administration takes place at home. The date, time and number of inhalations will be recorded. The compliance will be checked by the site staff at each planned visit.

A record of the number of Diskus inhalers dispensed to each subject and the number of actuation administered, read from the dose counter for each Diskus inhaler, must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.9. Treatment of Study Treatment Overdose

For this study, any dose of GSK2269557 >2000 µg within a 22 hour time period will be considered an overdose.

GSK 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 subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2269557 can no longer be detected systemically (at least 14 days for GSK2269557)
3) obtain a plasma sample for pharmacokinetic (PK) analysis within 7 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 subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Any clinical abnormalities identified during the conduct of the study will be locally managed by the Investigator.

6.11. Lifestyle and/or Dietary Restrictions

- Subjects must not sunbathe or use a tanning device (e.g. sunbed or solarium) whilst taking the study medication and until at least 2 weeks after their last dose. Subjects are to be advised that they should cover exposed areas of skin (e.g. use sun hat, long sleeves) and use a broad spectrum UVA/UVB sunscreen (SPF ≥30) on exposed areas of skin when outdoors.
- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.

- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit, and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

6.12.2. Prohibited Medications and Non-Drug Therapies

Regular or chronic treatment with medications that are considered strong inhibitors of CYP3A4 or CYP2D6 are not permitted. This includes anti-epileptic treatments, macrolide antibiotics, oral antifungal treatments (single doses and courses up to 7 days are allowed) and anti-tuberculous therapy. These medications must all have been stopped at least 14 days prior to first dose.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table (Screening and Follow Up Visits)

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Informed consent	X		
Demography	X		
Inclusion and exclusion criteria	X		
Full physical exam, including height and weight	X		
Brief physical examination, including weight		X	
Chest X-Ray	X		To be done before baseline HRCT to exclude significant pneumonia and other incidental serious underlying pathology.
Medical history (includes substance usage and Family history of premature CV disease)	X		Substances: Drugs, Alcohol, tobacco via history. No drug, alcohol screening is required.
Past and current medical conditions (including cardiovascular medical history and therapy history)	X		
Laboratory assessments (include Hematology and biochemistry)[1]	X	X	Historical values analysed by local lab to be used for eligibility assessment. Another sample must be collected and sent to central lab as soon as informed consent is obtained.
Hep B and Hep C screen[2]	X		
Urine pregnancy test (only WCBP)	X		Before conducting the HRCT. Done locally at the site.
12-lead ECG	X	X	Single assessment
Vital signs	X	X	Single assessment
HRCT (at TLC and FRC)	X		Within 48 h of diagnosis, if subject otherwise eligible. Includes electronic monitoring of breathing (if applicable). Baseline HRCT will be reviewed by the local site's radiologist to identify any significant occurring underlying medical conditions that require further clinical management or monitoring.
Induced Sputum[3]	X[4]		To include sputum culture pre-first dose. Culture to be done by the local site laboratory.

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Blood sample for mRNA Analysis	X[4]		Collected at any time on specified days
AE/SAE collection and review		X	
Concomitant medication review	X	X	

1. Due to the short screening window, central laboratory analysis results will not be available on time. Therefore the local laboratory results should be used for eligibility assessment (to exclude severe subjects and underlying medical conditions). If local laboratory results are already available from diagnosis of current exacerbation, there is no need to take another sample for local analysis. A sample for central laboratory analysis should also be obtained. See Section 7.8.6 for further details.
2. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required. Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor.

3. Induced sputum collection may be attempted on several occasions if an adequate sample is not produced at the first attempt.
4. To be collected at any time point before randomisation.

7.2. Time and Events Table (Treatment Period)

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
EFFICACY ASSESSMENTS							
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========					==========→	Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.
OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

1. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
2. Assessments do not need to be completed if screening assessments conducted within 48 hours
3. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
4. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

7.3. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

If they are being utilised in the study, Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

7.4. Biomarker(s)/Pharmacodynamic Markers

7.4.1. Pharmacodynamic Biomarkers in Sputum

- Collect sputum induction samples at the time-points shown in the time and events table (Section 7.1).
- The sputum induction collection process will follow local standard procedures and guidelines outlined in the SRM.
- The collection of induced sputum may be attempted on several occasions if an adequate sample is not produced at the first attempt.
- Further information on collection, processing, storage and shipping procedures are provided in the SRM.

7.4.2. mRNA in blood

- Collect 2.5 mL of blood into a PAXgene mRNA tube.

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

7.5. Patient diary

The subjects will be provided with a diary to record the following data when at home:

- Time and date of each dose administration and number of inhalations.

- Adverse Events and concomitant medications taken (including daily rescue medication – if used and how many times used).
- PEF from a handheld device. The best/highest result is recorded.

Changes in Health and details of any concomitant medications as well as PEF assessment details will be collected in the paper diaries and later transcribed into the CRF.

7.6. Genetics

Information regarding genetic research is included in Appendix 3.

7.7. Efficacy

7.7.1. Functional Respiratory Imaging

- A CT scan with a low radiation protocol at FRC and TLC will be conducted as listed in the Time and Events Table (Section 7.1). The same scanner should be used for baseline and post-treatment scans for an individual subject.
- A urine pregnancy test should be performed before the CT scan in female subjects of childbearing potential.
- Further information is provided in the SRM.

7.7.2. FEV_1 and FVC

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. These will be recorded as absolute values. The best/highest result is recorded.

- Further details are provided in the SRM.

7.7.3. Peak Expiratory Flow PEF

- PEF measurements will be taken (in triplicate) daily in the morning before dose administration, as soon as it is safe for the subject to do so. The best/highest result is recorded.
- Subjects will be provided with a handheld device.
- Further details are provided in the SRM.

7.8. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.8.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.8.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.8.1.3), at the time-points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.8.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.8.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

7.8.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

7.8.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless they meet the definition of an SAE as defined in Appendix 4 Exacerbations that meet the definition of an SAE will be recorded on the appropriate eCRF section and should be reported to GSK.

Medications used to treat a COPD exacerbation will be recorded in the exacerbation eCRF

7.8.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.8.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until the follow-up visit
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.8.3. Physical Exams

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

7.8.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.
- Three readings of blood pressure and pulse rate will be taken
- First reading should be rejected
- Second and third readings should be averaged to give the measurement to be recorded in the CRF.

7.8.5. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at screening and at each other timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

7.8.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Historical values (if the assessment was conducted as part of the standard of care) for blood gases, blood culture and sputum culture may also be collected if available.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Table 1 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential</u>:</td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose (non fasted)</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
<tr><td>CRP</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>• Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)</td></tr>
</table>

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 5.4.1 and Appendix 2
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Hematology and clinical chemistry at screening for excluding subjects with severe disease and uncontrolled medical conditions. The results of each test must be entered into the CRF.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Hematology, clinical chemistry and additional parameters to be tested are listed in Table 1.

7.9. Pharmacokinetics

7.9.1. Blood Sample Collection

A 2 mL blood samples for pharmacokinetic (PK) analysis of GSK2269557 will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.9.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK2269557 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for GSK2269557 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK/Scinovo, GlaxoSmithKline protocol.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

This study is designed to establish the PI3Kδ-dependent alterations in immune cell mechanisms related to neutrophil function as detected by changes in mRNA transcriptomics in samples of induced sputum from patients admitted with an exacerbation of COPD. The primary comparison will be between subjects treated with GSK2269557 in addition to standard of care, and subjects treated with placebo in addition to standard of care. In addition, treatment comparisons between subjects at baseline and subsequent time points will also be produced.

9.1. Sample Size Considerations

The sample size for this study has been based on feasibility. The sample size of 30 subjects completing the trial, with approximately 15 of which will receive GSK2269557 and 15 will receive placebo, is expected to be sufficient to provide a meaningful estimate of the mRNA alterations within the lungs.

Previous studies with similar sample size populations have yielded significant fold-changes (fold-change>1.5 and $p<0.05$) in immune cell mechanisms using the changes in mRNA transcriptomics.

Study Name	Sample	Study Design	Number of Subjects	Number of Differential probesets FC = >= 1.5, Pval <= 0.05	Notes
PII115117 FTIH Healthy Smoker nebulised GSK2269557	Sputum	Sputum N=12 3-way x-over placebo 400ug, 6400ug	12 (9 with all data points)	57 probesets change with both doses = 44 Genes	Gene changes relate predominantly to a down regulation of infection and inflammation responses. Link to Haemophilus influenzae and Moraxella catarrhalis infection biology – Identified prior to knowledge of Activated PI3Kδ Syndrome phenotype
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Sputum	Ex vivo Sputum incubated with GSK2269557 sampled at 6hrs (Sputum producers)	15 Subjects	490 probesets change vs vehicle control = 295 genes (of which 43 are dysregulated in COPD disease vs Healthy comparison)	43 genes altered in COPD and positively modulated by PI3Kδi GSK2269557. Biological themes in signature: Pro-cell movement/migration and cell viability, anti-apoptotic. Additionally link to B/T cell function. Signature supports GSK2269557 correction of neutrophil migration
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at 6hrs (Sputum	15 Subjects	19 probesets change vs vehicle control = 15 genes	Infection and inflammation associated genes
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at	15 Subjects	30 probesets change vs vehicle control = 25 genes	Infection and inflammation associated genes

9.1.1. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed in this study.

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Screened	• All subjects who were screened.	• Study Population
All subject	• All randomised subjects who receive at least one dose of the study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Pharmacodynamics • Safety • Efficacy
Pharmacokinetic	• Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.	• PK

9.2.2. Interim Analysis

No interim analyses will be performed.

9.3. Key Elements of Analysis Plan

9.3.1. Primary Analyses

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

Further details around the analysis of the mRNA data will be provided in the RAP.

9.3.2. Secondary Analyses

All secondary analyses will be described in full prior to unblinding in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)

- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure

there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
ECG	Electrocardiogram
FEV1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
GCP	ICH Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
PEF	Peak Expiratory Flow
PI3Kδ	Phosphoinositide 3-Kinase Delta
PK	Pharmacokinetic
QTcF	QT interval corrected using the Fridericia's formula
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SRM	Study Reference Manual
TLC	Total Lung Capacity
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DISKUS

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **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 subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (refer to Appendix 2). • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained 7 days after last dose[5] • 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

treatment and may continue subject in the study for any protocol specified follow up assessments	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form
MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • 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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, 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 subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. PK sample may not be required for subjects 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 blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.3. Appendix 3: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- COPD susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to

the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where 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.

12.4.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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 disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are 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

g. Is associated with liver injury and impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject'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 instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject 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 the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication

Pregnancy information on female partner of male study subjects

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks 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: Country Specific Requirements

No country-specific requirements exist.

12.7. Appendix 7: Protocol Amendment Changes

The amendment was created to remove the specific equations for the prediction of percent predicted from spirometry from the inclusion criteria (European Community of Coal and Steel and European Respiratory Society Global Lung Function Initiative reference equations (Quanjer 2012) in Section 7.7.2. At screening it may not be possible to identify which correction method was used, or modify the correction method used, at the time. As a result it may not be valid to stipulate that lung function values be corrected using any particular method. Both FEV_1 and FVC measurements (which are not entry criteria for the study) collected during the study will be collected as absolute values (uncorrected), so that consistency will be obtained across all sites in the study, and percent predicted will be calculated using a standard approach in house at the end of the study.

List of specific changes:

Page 22, Inclusion Criteria (#2 – Type of Subject and Diagnosis Including Disease Severity) - Third Bullet.

PREVIOUS TEXT

- The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted. Predictions should be according to the European Community of Coal and Steel (ECCS) equations OR the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012] and documented in the last 5 years.

REVISED TEXT

- The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted documented in the last 5 years.

Page 40, Section 7.7.2 (FEV_1 and FVC)

PREVIOUS TEXT

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. Predicted values will be based upon the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012].

REVISED TEXT

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. These will be recorded as absolute values. The best/highest result is recorded.

Page 54 – References

PREVIOUS TEXT

De Backer J, Vos W, Vinchurkar S, Van Holsbeke C, Poli, G, Claes R et al. The Effect of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Fundtional Respiratory Imaging. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:1-12.

De Backer LA, Vos WG, Salgado R, De Backer JW, Devoldr A, Verhulst SL et al. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD. *International Journal of COPD.* 2011;6:637-646.

De Backer Lieve A, Vos Wim, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. *Eur Respir J.* 2012;40:298-305.

GlaxoSmithKline Document Number 2012N141231_04: GSK2269557 Investigator's Brochure. Report Date 12-FEB-2015.

Goldin J, Tashkin D, Kleerup E, Greaser MS, Haywood U, Sayre J et al. Comparative effects of hydrofluoroalkane and chloroflurocarbon beclomethasone dipropionate inhalation on small airways: Assessment with functional helical thin-section computed tomography. *J Allergy Clin Immunol.* 1999;104 #6:S258-S267.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(a):24. Table 3-2.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D et al. *Contraceptive Technology.* 19th ed. New York:Ardent Media; 2007(b): 28.

ICRP. 2007 Recommendation of the International Commission on Radiological Protection. *ICRP Publication 103.* 2007;37:2-4.

Kim SR, Lee KS, Park HS, et al. HIF -1 alpha inhibition ameliorates an allergic airway disease via VEGF suppression in bronchial epithelium. *Eur J Immunol.* 2010;40 (10):2858-69.

Okkenhaug K, Aki K, Vanhaesebroeck B. Antigen receptor signalling: A distincive role for the p110 isoform of PI3K. *Trends in Immunuology.* 2007;28:80-7.

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Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI13K delta in neutrophil inflammatory responses. *Biochem Biophys Res Commun.* 2003 Sep 5;308 (4):764-9.

Weisser SB, McLarren KW, Voglmaier B, et al. Alternative activation of macrophages by IL-4 requires SHIP degradation. *Eur J Immunol.* 2011;41(6):1742-53.

REVISED TEXT

De Backer J, Vos W, Vinchurkar S, Van Holsbeke C, Poli, G, Claes R et al. The Effect of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Fundtional Respiratory Imaging. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2014;27:1-12.

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De Backer Lieve A, Vos Wim, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. *Eur Respir J.* 2012;40:298-305.

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Kim SR, Lee KS, Park HS, et al. HIF -1 alpha inhibition ameliorates an allergic airway disease via VEGF suppression in bronchial epithelium. *Eur J Immunol.* 2010;40 (10):2858-69.

Okkenhaug K, Aki K, Vanhaesebroeck B. Antigen receptor signalling: A distincive role for the p110 isoform of PI3K. *Trends in Immunuology.* 2007;28:80-7.

Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI13K delta in neutrophil inflammatory responses. *Biochem Biophys Res Commun.* 2003 Sep 5;308 (4):764-9.

Weisser SB, McLarren KW, Voglmaier B, et al. Alternative activation of macrophages by IL-4 requires SHIP degradation. *Eur J Immunol.* 2011;41(6):1742-53.

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Compound Number: GSK2269557

Development Phase IIA

Effective Date: 04-JUN-2015

Author(s): PPD (CCSE); PPD (CPSSO); PPD (Respiratory CEDD); PPD (Exp Biology); PPD (Clinical Statistics); PPD (CPMS); PPD (GCSP).

SPONSOR SIGNATORY:

PPD

Steven Pascoe
VP TA Clinical Development Leader

04-JUNE-2015
Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD				Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
Secondary Medical Monitor					Discovery Medicine Respiratory CEDD GlaxoSmithKline Gumnnels Wood Rd. Stevenage, Herts, SG1 2NY
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201928

Rationale

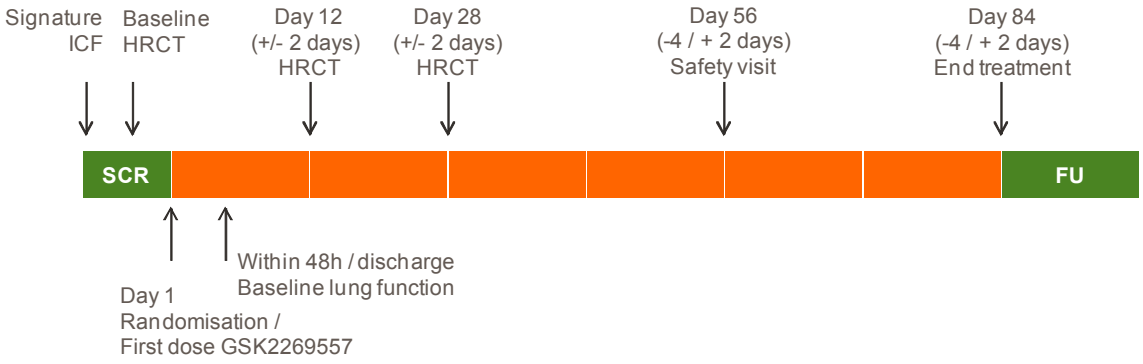
Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Haematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD.	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD compared to placebo.	• PEF • Reliever usage • $FEV_{1\ and}$ FVC at clinic prior to sputum induction
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral

Objectives	Endpoints
administered to subjects with acute exacerbation of COPD, compared to placebo.	qPCR.
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment

Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual Chronic Obstructive Pulmonary Disease (COPD) medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The High-Resolution Computed Tomography (HRCT) scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (± 2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table. Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7-14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

Type and Number of Subjects

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected numbers of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

Analysis

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

2. INTRODUCTION

GSK2269557 is a potent and highly selective inhaled Phosphoinositide 3-Kinase Delta (PI3Kδ) inhibitor being developed as an anti-inflammatory and anti-infective agent for the treatment of inflammatory airways diseases.

2.1. Study Rationale

The purpose of this study is to evaluate specific alterations in immune cell mechanisms related to neutrophil function as detected by PI3Kδ-dependent changes in mRNA extracted from induced sputum in patients experiencing an exacerbation of COPD. In addition this study will also further evaluate the plasma PK and assess the safety of GSK2269557 administered to patients diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD). The efficacy of treatment with GSK2269557 will also be measured using functional respiratory imaging (FRI) and spirometry.

This study will also explore the pharmacodynamic effects of once daily repeat doses of inhaled GSK2269557 on cytokines, mediators and microbiome in induced sputum samples. These will be obtained from subjects at entry, during their exacerbation, and at additional time points over the 12 week treatment period. To understand patient efficacy, at entry, Day 12 and Day28 the sputum biomarker data will be correlated with computed tomography (CT).

2.2. Brief Background

PI3Kδ is a member of the Class IA family of phosphoinositides 3-kinases (PI3Ks) that convert the membrane phospholipid phosphatidylinositol 4,5-biphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is a second messenger in many cellular processes including cell growth, differentiation and migration. PI3Kδ has specific roles in mediating antigen receptor and cytokine signalling in T-cells, mast cells and B-cells [Okkenhaug, 2007] and roles in neutrophil chemotaxis and activation [Sadhu, 2003]. A PI3Kδ inhibitor has the potential to inhibit major cell types responsible for the inflammation associated with both COPD and asthma.

In COPD, tobacco smoke or other irritants activate epithelial cells and macrophages to release inflammatory mediators such as chemokines that attract neutrophils and T cells to the lungs. PI3Kδ is thought to play a role in a number of epithelial responses relevant for the development of COPD. Therefore a PI3Kδ inhibitor may be able to suppress a number of these processes [Kim, 2010]. A greater proportion of macrophages appear to be alternatively activated in COPD and their ability to phagocytose infective pathogens is reduced as a result of this alternative activation. PI3Kδ is one of the mediators involved in determining this alternative phenotype in macrophages and therefore it is proposed that inhibition of PI3Kδ might rebalance macrophage activation towards a classic phagocytic phenotype [Weisser, 2011] facilitating clearance of bacteria, a major cause of exacerbation in COPD. The neutrophil and T cell are the two major inflammatory cell types involved in the pathogenesis of COPD and both are targeted by PI3Kδ inhibitors.

GSK2269557 has demonstrated the ability to protect against and control bacterial infections in preclinical rodent models. This is coupled with recent observations that PI3Kδ inhibition leads to a correction in vitro of aberrant neutrophil chemotaxis directionality in the blood of COPD patients. Furthermore, a human point mutation which results in a constitutively activated version of PI3Kδ has recently been characterised where the majority of affected patients have recurrent lung infections with the same bacterial species which are seen in COPD patients and are known to drive exacerbations. Collectively these data suggest that repeat dosing with GSK2269557 could potentially reduce the impact of an acute exacerbation, or prevent the onset of a secondary bacterial exacerbation or recurrent exacerbation.

Proinflammatory cytokines were reduced by GSK2269557, both in preclinical rodent bacterial models, and COPD patient samples treated in vitro and in the study setting (PII115119).

GSK2269557 has been administered as single and repeat doses to healthy subjects as nebulized solution in the FTIH study PII115117 up to a dose of 6400 µg per day for 7 days. GSK2269557 has also been administered as single and repeat doses to healthy smokers as a dry powder formulation in study PII116617 up to a dose of 3000 µg as single dose and 2000 µg per day for 14 days. GSK2269557 has been well tolerated across the range of doses used. There is also an ongoing study (Study PII115119, non-reported) where a total daily dose of up to 2000 µg of GSK2269557 is being administered to stable COPD patients via a dry powder inhaler for 14 days in a two part study. Part A of this study has completed and Part B will characterise the steady-state (exposure) dose response following repeat inhaled doses of up to 2000µg for the same treatment duration. There is also an on-going larger clinical study PII116678 which is almost identical in design to 201928 using 1000 µg of GSK2269557 per day administered via a Diskus dry powder inhaler to patients diagnosed with an acute exacerbation of COPD. For simplicity study PII116678 does not capture induced sputum hence cannot analyse any changes in mRNA. The primary objective of the current study is to capture induced sputum to enable the mRNA analysis on a smaller cohort.

More information about the non-clinical and clinical studies is available in the GSK2269557 Investigator's Brochure (IB) GlaxoSmithKline Document Number 2012N141231_04.

2.2.1. Use of mRNA transcriptomics by Affymetrix

Analysis of changes in mRNA can be used to demonstrate alterations in biochemical pathways at the gene transcription level. This can be used to better understand the consequences of drug intervention on disease pathophysiology, and ultimately predict alterations which could translate to a positive clinical benefit for patients. Messenger RNA can be extracted from a variety of biological samples (including induced sputum and blood) taken from patients before and after drug dosing to show the impact a drug is having.

The advantage of using Affymetrix is the broad (~50k) gene set covered using this technology enabling great depth in exploring the biological consequences of drug

intervention. This technology has been used in previous preclinical and clinical studies using GSK2269557 generating a fingerprint of PI3Kδ inhibition in disease. Importantly these approaches allow areas of complex PI3Kδ-dependent immune cell mechanisms and pathophysiology, specifically related to neutrophil function to be explored which are not easily quantified using other techniques.

2.2.2. Use of HRCT Endpoints to characterise Lung Function

High-resolution computed tomography (HRCT) scans provide a highly detailed insight into the structure and architecture of the respiratory system. A clear distinction can be made between the lung parenchyma, the intraluminal air and alveolar spaces up to the level of the smaller airways with a diameter of 1-2mm. To model dynamic information, low dose HRCT scans can be taken at two lung volumes: after deep inhalation (total lung capacity or TLC) and after normal expiration (functional residual capacity or FRC). The patient's breathing is monitored in real time during the scans to ensure the correct lung levels are scanned. Due to the natural contrast between the intraluminal air and the surrounding tissue, it is possible to attain a significant reduction in radiation dose (1-2 mSv per scan) compared to standard CT protocols (>4 mSv per scan) by reducing the tube current and the voltage. Depending on the patient's weight, a 6- to 10-fold reduction can be obtained per scan without losing image quality. As a comparison, in the USA, the average annual background radiation exposure is 6.2 mSv and a transatlantic flight results in 0.07 mSv exposure.

The high resolution images allow for a three dimensional reconstruction of the airway tree and vasculature by applying segmentation principles. These three dimensional models can be used to measure airway dimensions as well as potentially allowing the phenotyping of patients by disease severity. The three dimensional computer reconstructions can be used for fluid dynamic modelling. This method is used to simulate flow through these airway models and determine the typical flow characteristics such as local pressure drops, velocities and resistance. It can also be used to predict particle deposition in the airways of these patients when using inhaled drug products.

This method consisting of 2 low dose HRCT scans at several time points has previously been used successfully in clinical trials involving COPD patients [De Backer, 2011; De Backer, 2012; De Backer, 2014; Goldin, 1999].

3. OBJECTIVE(S) AND ENDPOINT(S)

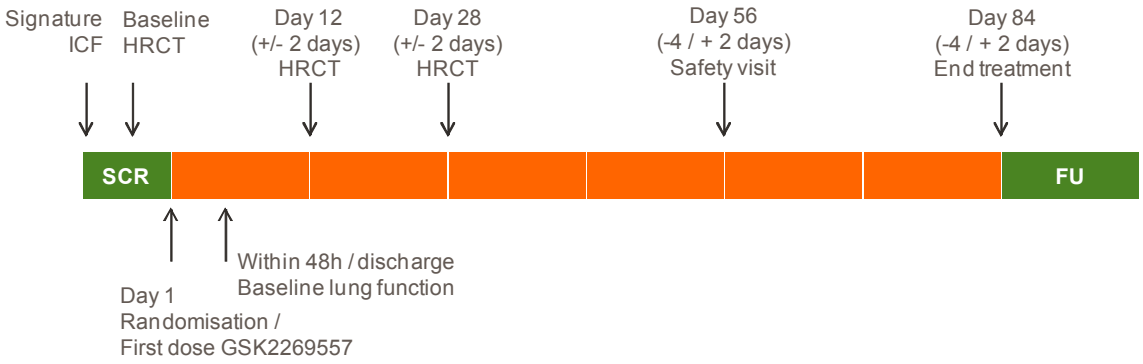
Objectives	Endpoints
Primary	
• To establish the PI3Kδ-dependent changes in previously identified immune cell mechanisms specifically related to neutrophil function using mRNA in sputum from patients with an exacerbation of COPD, with or without treatment with GSK2269557.	• Alterations in previously identified immune cell mechanisms specifically related to neutrophil function as determined by changes in mRNA transcriptomics in induced sputum after 12, 28 and 84 days of treatment.
Secondary	
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung parameters derived from HRCT scans in subjects with acute exacerbation of COPD, compared to placebo	• Change from baseline in siVaw, iVaw, iRaw, siRAW, total lung capacity, lung lobar volumes, trachea length and diameter at FRC and TLC after 12 days of treatment and after 28 days of treatment.
• To assess the safety and tolerability of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Adverse events • Hematology, clinical chemistry • Vital signs • 12-lead ECG
• To evaluate the plasma PK of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD	• Day 1 plasma Cmax and trough (24 hours) post dose for inpatients • Trough concentration after 12 days, 28 days, 56 days and 84 days of treatment.
• To evaluate the effect of once daily repeat inhaled doses of GSK2269557 on lung function parameters in subjects with acute exacerbation of COPD, compared to placebo	• PEF, Reliever usage. • FEV_1 and FVC at clinic prior to sputum induction.
Exploratory	
• To establish any other PI3Kδ-dependent changes in mRNA in sputum or blood from patients with an exacerbation of COPD, with or without treatment with GSK2269557. • To explore the pharmacodynamic effects in induced sputum of once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to	• Alterations in immune cell mechanisms as determined by changes in mRNA transcriptomics in induced sputum or blood after 12, 28 and 84 days of treatment. • Endpoints may include, but not limited to cytokines (IL-6, IL-8, TNFα), microbiome (by 16SrRNA), bacterial qPCR, viral qPCR.

Objectives	Endpoints
placebo.	
• To assess the changes in other CT parameters such as low attenuation score after once daily repeat inhaled doses of GSK2269557 administered to subjects with acute exacerbation of COPD, compared to placebo.	• Change from baseline for other CT parameters including low attenuation score after 12 days of treatment and after 28 days of treatment.

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind, placebo-controlled, parallel-group study. All subjects will continue on their usual COPD medications throughout the entire duration of the study regardless of treatment arm assignment. Subjects will be on standard of care treatment (antibiotic and corticosteroids) upon diagnosis of a COPD exacerbation.



4.2. Treatment Arms and Duration

Subjects will be required to participate in the following:

Screening: Following diagnosis during outpatient assessment by a Respirologist, Emergency Department visit or acute admission to hospital, and up to 3 days before start of study treatment. During this time:

- The start of the standard of care (to include both antibiotics and corticosteroids) is expected to start shortly after diagnosis, though it is allowed to have already been started before the formal diagnosis of COPD exacerbation is made.

- The HRCT scan should be conducted at the earliest opportunity after obtaining Informed Consent from the subject and within 48 h of diagnosis by a Respirologist or physician with respiratory experience.

- Randomisation and first dose administration should take place as soon as possible following HRCT scan assessment has been performed and no later than 24h after completing the HRCT scan.

Treatment period: Once daily study treatment administration will start on Day 1 (visit 1).

- For subjects who were hospitalized:
    - If discharge takes place before Day 10, the subject must complete the assessments planned for visit 2 on discharge and must then visit the unit on Day 12 (±2 days) (visit 3).
    - If discharge takes place between Day 10 and Day 14 (inclusive), the assessments planned for visit 2 and visit 3 may be completed on the day of discharge.
    - If discharge takes place from Day 15 (inclusive), the assessments planned for visit 2 and visit 3 should be completed as soon as it is safe for the patient to do so.
- For subjects who were not hospitalized: the subject must complete the assessments planned for visit 2 within 48 hours of start of treatment, and must then visit the unit on Day 12 (±2 days) to complete the assessments planned for visit 3.

Subjects will then dose at home until Day 84 (– 4 / + 2 days), with the exception of the days when subjects come to the clinic. On those days, they will dose at the clinic. On Day 12 (± 2 days) (unless visit completed on discharge), Day 28 (± 2 days), Day 56 (– 4 / + 2 days) and Day 84 (– 4 / + 2 days) subjects will return on an outpatient basis to complete the assessments described in the Time & Event table (Section 7.1). Subjects will be discharged once all assessments have been performed and there are no safety concerns.

Follow up: 7 to 14 days after last dose.

The total duration of the study is 13-14 weeks including the screening visit.

4.3. Type and Number of Subjects

Approximately 35 subjects with an acute exacerbation of COPD will be randomized such that approximately 15 subjects on active and 15 subjects on placebo provide sputum at all the scheduled time points and complete the study. If a higher than expected number of subjects prematurely discontinue the study, or fail to produce sufficient sputum post randomisation additional subjects may be randomised at the discretion of the sponsor.

4.4. Design Justification

This study will include a placebo control to allow for a valid evaluation of the pharmacodynamic endpoints and adverse events attributable to treatment versus those

independent of treatment. Subjects will also receive standard of care for their exacerbation and throughout the study.

4.5. Dose Justification

The dose chosen for this study is 1000 µg of GSK2269557 per day administered via a dry powder inhaler for a duration of 84 days (– 4 / + 2 days). This dose has been selected based on previous safety and tolerability data in man (healthy subjects and COPD subjects) as well as demonstration of target (PI3Kδ) inhibition by observed changes in biomarkers. Together with an additional study to be run in parallel (PII116678), this dose of GSK2269557 is being dosed to subjects in PII116678 with an exacerbation of COPD, so it will be assumed for exposure predictions, unless otherwise stated, that these subjects will have a similar lung deposition, distribution and plasma exposure to that of the healthy volunteers. However it is accepted that these types of subjects may have reduced airway conductance and hence likely reduced deposition. This can be appropriately defined in this study based on the actual plasma exposures achieved.

Twice this dose level (2000 µg) using the same formulation has previously been given once daily to healthy male smokers for 14 days (study PII116617). There is also an ongoing study where a total daily dose of 1000 µg of GSK2269557 is administered to stable COPD subjects via a dry powder inhaler for 14 days (study PII115119) which at the time of writing of this protocol had successfully dosed 21 subjects on active treatment and collected pharmacokinetics (PK) samples for analysis out to 14 days.

The target effect compartment for PI3Kδ inhibition is the intracellular compartment of the immune cells resident in the lung tissue and lumen. GSK2269557 has a high potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL) which translates into an IC_{50} in a more complex system (PHA stimulated lung tissue) of approximately 120 ng/mL (or 2.5 ng/mL free unbound drug). Based on the measured steady-state cellular concentration of GSK2269557 collected at trough (24 h) from the lungs of healthy smokers at 2000 µg DPI (450 ng/mL) in the clinical study it is expected that at 1000 µg (225 ng/mL), concentrations will be sufficient and PI3Kδ inhibition maintained in the lung at ≥ 90% inhibition for 24 h.

Target PI3Kδ inhibition is based on a wide range of pharmacology experiments. Details of these as well as the pharmacokinetics and safety data can be found in the IB, [GlaxoSmithKline Document Number: 2012N141231_04].

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2269557 can be found in the IB [GlaxoSmithKline Document Number 2012N141231_04]. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2269557]		
Bronchospasm Mucosal irritancy	A general risk with Inhaled treatment Detected in 13 week toxicology study in the dog	Subjects will be allowed to continue regular COPD treatments and have standard of care for treatment of their exacerbation. More severe patients will have their treatment started in hospital. Patients will be regularly monitored for AEs and a patient diary kept. Thus far this has not been seen in clinical studies.
Potential photosensitivity	In the absorption spectrum for GSK2269557 there are peaks at the boundary of the ultraviolet (UV) light [UVA/UVB] region with a lambda max at 320 nm (molar extinction coefficient 43800 L/Mol/cm), with smaller peaks at 305 nm and 332 nm.	Subjects will be advised to take UV protection measures (see Section 6.11).
Study Procedures		
Radiation risk as part of HRCT scans	The maximum amount of radiation dose a patient undergoing all six scans will receive is approximately 12mSv. Six low dose HRCT scans (one at TLC and FRC on screening, Day 12 and Day 28 visits) at are required throughout the study for the functional imaging protocol	Reduced tube voltage (100 kV), and tube current are used. Scanning time less than 5 s per scan. Total radiation dose for a total of six CT scans will be approximately 12mSv. Final radiation dose will be dependent on the patient weight, with a range of between 1-2mSv per scan per patient. This radiation dose falls into the International Commission on Radiological Protections [ICRP, 2007] category IIb (minor to intermediate risk).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		The outcomes of this study will provide information which would produce advances in knowledge, leading to a potential health benefit in the future for patients in this target population. The CT may also provide information for the patients general clinical management
Sputum induction	Standard sputum induction techniques using hypertonic saline can result in bronchospasm and therefore could potentially induce bronchospasm in a patient or impact a pre-existing exacerbation..	For patients during an exacerbation and for sputum induction during the recovery period, including the day 28 visit, patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant). Sputum induction will only be carried out using Normal (0.9%) saline, which is also often used in patients clinically to facilitate sputum clearance. For the final sputum induction patients will be pre-dosed with nebulised or inhaled beta-2-agonist (or ipratropium bromide if beta-2-agonist intolerant) and the induction carried out with 0.9% saline initially and only then followed by hypertonic (3-5%) if required, and, in the opinion of the Investigator, it is considered safe to do so.

4.6.2. Benefit Assessment

The outcomes of this study will provide information which will produce advances in knowledge of the pathophysiology of COPD exacerbations, leading to a potential health benefit in the future for patients in this target population. The CT scan may also provide information for the patient's general clinical management.

4.6.3. Overall Benefit:Risk Conclusion

The overall benefit:risk is considered to be positive. There is an opportunity to determine if there may be a new drug developable for the treatment of acute exacerbations of COPD which has not seen any new treatments recently. The scientific value in obtaining functional CT information on the anatomy and pathophysiology of COPD exacerbations and how the lung responds to therapy will be extremely valuable to the wider clinical community and justifies the limited radiation exposure (maximum 12 mSv in total) from the CT scan procedures. The CT will also be useful to provide clinical information about the patient for the patient's physician and contribute to clinical management.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number: 2012N141231_04]

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

[1] AGE
• Between 40 and 80 years of age inclusive, at the time of signing the informed consent.
[2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
• The subject has a confirmed and established diagnosis of COPD, as defined by the GOLD guidelines for at least 6 months prior to entry. • The subject is able to produce >100 mg of sputum at screening for processing, (ie, total weight of sputum plugs.). • The subject has a post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \leq 80$ % of predicted. Predictions should be according to the European Community of Coal and Steel (ECCS) equations OR the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012] and documented in the last 5 years. • Disease severity: Acute exacerbation of COPD requiring an escalation in therapy to include both corticosteroid and antibiotics. Acute exacerbation to be confirmed by an experienced physician and represent a recent change in at least two major and one minor symptoms, one major and two minor symptoms, or all 3 major symptoms. Major symptoms: • Subjective increase in dyspnea • Increase in sputum volume • Change in sputum colour Minor symptoms: • Cough • Wheeze • Sore throat • The subject is a smoker or an ex-smoker with a smoking history of at least 10 pack years (pack years = (cigarettes per day smoked/20 x number of years smoked)).

[3] WEIGHT
• Body weight ≥ 45 kg and body mass index (BMI) within the range 18 – 32 kg/m^2 (inclusive).

[4] SEX

- Male
- Female subject : is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

1. Non-reproductive potential defined as:

Pre-menopausal females with one of the following:

Documented tubal ligation

Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion

Hysterectomy

Documented Bilateral Oophorectomy

Postmenopausal defined as 12 months of spontaneous amenorrhea. Females whose menopausal status is in doubt will be required to use, or have been using, one of the highly effective contraception methods as specified below from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

2. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication and until completion of the follow-up visit.

GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

1. Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label
2. Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]
3. Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
4. Injectable progestogen [Hatcher, 2007a]
5. Contraceptive vaginal ring [Hatcher, 2007a]
6. Percutaneous contraceptive patches [Hatcher, 2007a]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject

[Hatcher, 2007a].

8. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Specific inclusion criteria for Male subjects with female partners of reproductive potential is outlined below:

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until after the completion of the follow up visit.

1. Vasectomy with documentation of azoospermia.
2. Male condom plus partner use of one of the contraceptive options below:

Contraceptive subdermal implant that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label

Intrauterine device or intrauterine system that meets GSK standard criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]

Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
Injectable progestogen [Hatcher, 2007a]

Contraceptive vaginal ring [Hatcher, 2007a]

Percutaneous contraceptive patches [Hatcher, 2007a]

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

[5] INFORMED CONSENT
• Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

• To avoid recruitment of subjects with a severe COPD exacerbation, the presence of any one of the following severity criteria will render the subject ineligible for inclusion in the study:
  • Need for invasive mechanical ventilation (short term (< 48h) NIV or CPAP is acceptable)
  • Haemodynamic instability or clinically significant heart failure
  • Confusion
  • Clinically significant pneumonia, identified by chest X-ray at screening, and as judged by the Investigator.
• Subjects who have current medical conditions or diseases that are not well controlled and, which as judged by the Investigator, may affect subject safety or influence the outcome of the study. (Note: Patients with adequately treated and well controlled concurrent medical conditions (e.g. hypertension or NIDDM) are permitted to be entered into the study).
• Subject has a diagnosis of active tuberculosis, lung cancer, clinically overt bronchiectasis, pulmonary fibrosis, asthma or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the subject or affect the interpretation of the results.
• ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
• A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the exclusion criteria, outside of the reference range for the population being studied may be included if the Investigator [in consultation with the GSK Medical Monitor if required] documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
• Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
• ECG indicative of an acute cardiac event (e.g. Myocardial Infarction) or demonstrating a clinically significant arrhythmia requiring treatment.
• QTcF > 450 msec or QTcF > 480 msec in subjects with Bundle Branch Block, based on single QTcF value.
• Subjects who have undergone lung volume reduction surgery.

[2] CONCOMITANT MEDICATIONS
• Subject is currently on chronic treatment with macrolides or long term antibiotics. • Subject is being treated with long term oxygen therapy - LTOT (> 15 hours/day). • The subject has been on chronic treatment with anti-Tumour Necrosis Factor (anti-TNF), or any other immunosuppressive therapy (except corticosteroid) within 60 days prior to dosing.

[3] RELEVANT HABITS
• History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >28 units for males or >21 units for 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.

[4] CONTRAINDICATIONS
• History of sensitivity to any of the study medications, or components thereof (such as lactose) or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

[5] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
• A known (historical) positive test for HIV antibody. • Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. NOTE: Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor. • Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. • The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). • Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria Protocol Deviations, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

Subjects who are withdrawn from treatment will also be withdrawn from the study.

If a higher than expected number of subjects prematurely discontinues the study, additional subjects may be randomised and assigned to the same treatment sequence, at the discretion of the Sponsor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

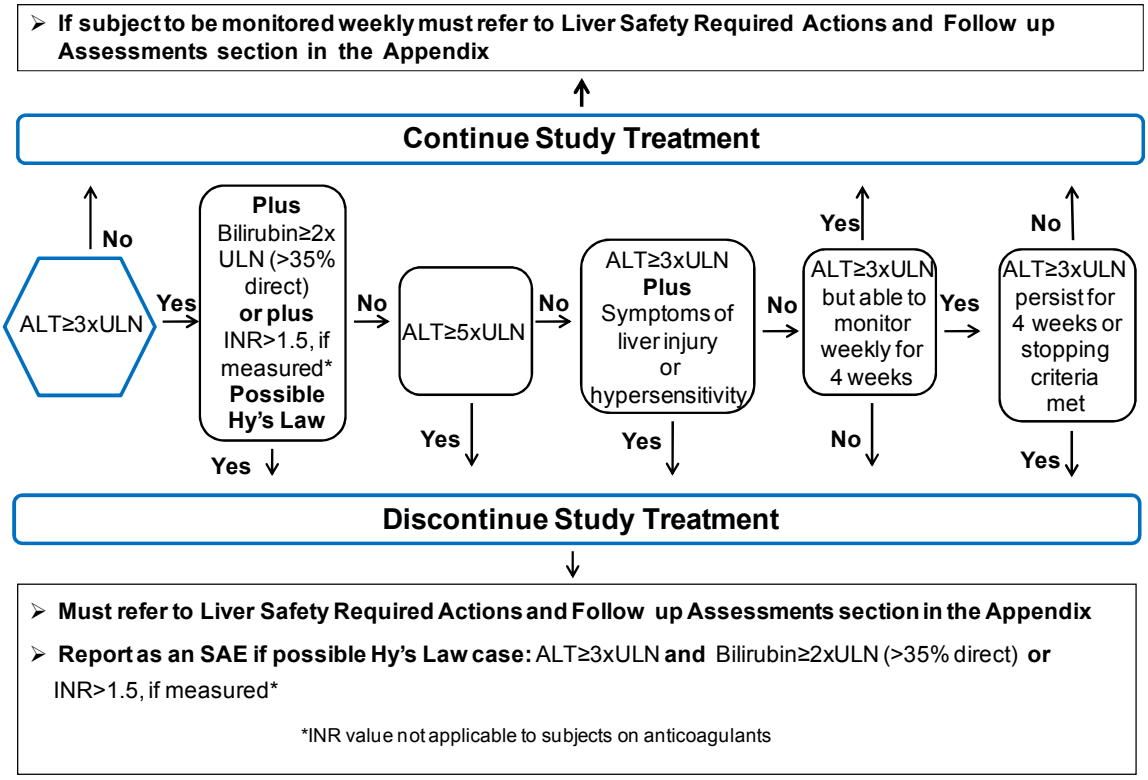
Subjects who are withdrawn should complete the assessments planned for the follow up visit.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

5.4.1.1. Study Treatment Restart or Re-challenge

Study treatment restart or re-challenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.2. QTc Stopping Criteria

- QTcF should be based on averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. For example, if an ECG (Electrocardiogram) demonstrates a prolonged QTcF interval, obtain two more ECGs and use the averaged QTcF values of the three ECGs to determine whether the patient should be discontinued from the study.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTcF >500 msec OR Uncorrected QT >600 msec

- Change from baseline of QTcF > 60 msec

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

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

5.4.3. Other Stopping Safety Criteria

For an individual study participant, stopping criteria include, but are not limited to:

Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests, spirometry assessments, etc), as judged by the Principal Investigator in consultation with the Medical Monitor if necessary.

Treatment failure or recurrent exacerbation does **not** mandate withdrawal from the study, unless there is a safety concern as judged by the Investigator, in consultation with the Medical Monitor if necessary.

Subjects should be withdrawn from the study if confusion, acute respiratory acidosis (pH < 7.30), or need for invasive mechanical ventilation occurs.

5.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment	
Product name:	GSK2269557	Placebo
Formulation description:	Lactose blend containing GSK2269557 in Diskus™ device	Lactose in Diskus™ device
Dosage form:	Dry powder for inhalation	Dry powder for inhalation
Unit dose strength(s)/Dosage level(s):	500 µg / blister	N/A
Route of Administration	Inhalation	Inhalation
Dosing instructions:	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.	2 inhalations to be taken every day before breakfast (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for approximately 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart.

6.2. Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Central based randomisation will be used.

Subjects will be randomised to treatments A or B where:

A = Placebo

B = GSK2269557 1000 µg

A web based interactive response system will be used to assign subjects to treatment.

6.3. Planned Dose Adjustments

If adverse events, unrelated to COPD exacerbation, which are of moderate or severe intensity and are consistent across subjects in the group, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK2269557, are observed in more than 30% of the subjects then the study will be halted and no further subject will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the Ethics Committees will then take place prior to any resumption of dosing. If the above is observed consideration may be given to reducing the dose of GSK2269557 to 500 µg O.D.

6.4. Subject Specific Dose Adjustment Criteria

There are no subject specific dose adjustment criteria.

6.5. Blinding

This will be a double blind study and the following will apply.

- The investigator or treating physician may un-blind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** un-blinding the subject's treatment assignment.
- If GSK personnel are not contacted before the un-blinding, the investigator must notify GSK as soon as possible after un-blinding.
- The date and reason for the un-blinding must be fully documented in the Case Report Form (CRF)
- A subject will be withdrawn if the subject's treatment code is un-blinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the un-blinding) will be recorded in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may un-blind the treatment assignment for any subject with a Serious Adverse Event (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 subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.7. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects 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 labelled 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 (i.e. receipt, reconciliation and final disposition records).

- Further guidance and information for 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.

6.8. Compliance with Study Treatment Administration

When subjects 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 subjects will be asked to complete a diary when dose administration takes place at home. The date, time and number of inhalations will be recorded. The compliance will be checked by the site staff at each planned visit.

A record of the number of Diskus inhalers dispensed to each subject and the number of actuation administered, read from the dose counter for each Diskus inhaler, must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.9. Treatment of Study Treatment Overdose

For this study, any dose of GSK2269557 >2000 µg within a 22 hour time period will be considered an overdose.

GSK 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 subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK2269557 can no longer be detected systemically (at least 14 days for GSK2269557)
3) obtain a plasma sample for pharmacokinetic (PK) analysis within 7 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 subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

Any clinical abnormalities identified during the conduct of the study will be locally managed by the Investigator.

6.11. Lifestyle and/or Dietary Restrictions

- Subjects must not sunbathe or use a tanning device (e.g. sunbed or solarium) whilst taking the study medication and until at least 2 weeks after their last dose. Subjects are to be advised that they should cover exposed areas of skin (e.g. use sun hat, long sleeves) and use a broad spectrum UVA/UVB sunscreen (SPF ≥30) on exposed areas of skin when outdoors.
- Subjects should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, exotic citrus fruits or grapefruit hybrids from first dose till the end of the study.
- Subjects should abstain from alcohol on the day when they visit the clinical unit and until their discharge on that day.
- Subjects should refrain from smoking for at least 2 hours prior to each pulmonary function test conducted at the clinical unit/site.

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

On entry to the study all treatment required for standard of care and additional medical problems is permitted to start and continue.

The subjects are allowed to continue their regular COPD treatments for the duration of the study. However, the subjects should refrain, if possible, from using relief bronchodilators for at least 4 hours prior to each spirometry conducted at the clinical unit,

and HRCT scan assessment unless essential for clinical symptom relief. Otherwise free use of reliever/rescue medication is allowed. Rescue ventolin and aerochambers may be provided by GSK for this study.

All prior (up to 2 months prior to screening) and concomitant medications should be recorded in the subject's CRF.

6.12.2. Prohibited Medications and Non-Drug Therapies

Regular or chronic treatment with medications that are considered strong inhibitors of CYP3A4 or CYP2D6 are not permitted. This includes anti-epileptic treatments, macrolide antibiotics, oral antifungal treatments (single doses and courses up to 7 days are allowed) and anti-tuberculous therapy. These medications must all have been stopped at least 14 days prior to first dose.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table (Screening and Follow Up Visits)

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Informed consent	X		
Demography	X		
Inclusion and exclusion criteria	X		
Full physical exam, including height and weight	X		
Brief physical examination, including weight		X	
Chest X-Ray	X		To be done before baseline HRCT to exclude significant pneumonia and other incidental serious underlying pathology.
Medical history (includes substance usage and Family history of premature CV disease)	X		Substances: Drugs, Alcohol, tobacco via history. No drug, alcohol screening is required.
Past and current medical conditions (including cardiovascular medical history and therapy history)	X		
Laboratory assessments (include Hematology and biochemistry)[1]	X	X	Historical values analysed by local lab to be used for eligibility assessment. Another sample must be collected and sent to central lab as soon as informed consent is obtained.
Hep B and Hep C screen[2]	X		
Urine pregnancy test (only WCBP)	X		Before conducting the HRCT. Done locally at the site.
12-lead ECG	X	X	Single assessment
Vital signs	X	X	Single assessment
HRCT (at TLC and FRC)	X		Within 48 h of diagnosis, if subject otherwise eligible. Includes electronic monitoring of breathing (if applicable). Baseline HRCT will be reviewed by the local site's radiologist to identify any significant occurring underlying medical conditions that require further clinical management or monitoring.
Induced Sputum[3]	X[4]		To include sputum culture pre-first dose. Culture to be done by the local site laboratory.

Procedure	Screening (up to 3 days prior to Visit 1)	Follow-up (7-14 days post-last dose)	Notes
Blood sample for mRNA Analysis	X[4]		Collected at any time on specified days
AE/SAE collection and review		X	
Concomitant medication review	X	X	

1. Due to the short screening window, central laboratory analysis results will not be available on time. Therefore the local laboratory results should be used for eligibility assessment (to exclude severe subjects and underlying medical conditions). If local laboratory results are already available from diagnosis of current exacerbation, there is no need to take another sample for local analysis. A sample for central laboratory analysis should also be obtained. See Section 7.8.6 for further details.
2. If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required. Because of the short window for screening, treatment with GSK2269557 may start before receiving the result of the hepatitis tests. If subsequently the test is found to be positive, the subject may be withdrawn, as judged by the Principal Investigator in consultation with the Medical Monitor.

3. Induced sputum collection may be attempted on several occasions if an adequate sample is not produced at the first attempt.
4. To be collected at any time point before randomisation.

7.2. Time and Events Table (Treatment Period)

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
SAFETY ASSESSMENTS							
AE/SAE collection and review	←==========→						
Concomitant medication review	←==========→						
Reliever usage	←==========→						
Brief physical exam, including weight	X[2]		X	X	X	X	Pre-dose
Laboratory assessments (include haematology and biochemistry)	X[2]		X	X	X	X	Pre-dose
12-lead ECG	X[2]		X	X	X	X	Pre-dose. Single assessment
Vital signs	X[2]		X	X	X	X	Pre-dose. Single assessment
Urine pregnancy test (only WCBP)			X	X			Before conducting the HRCT
STUDY TREATMENT							
Randomisation	X						
Study drug administration	←==========→						Daily in the morning before breakfast, (with the exception of days when the subjects have a planned visit to the clinic. On those days, they will be dosed at the clinic).
Assessment of study treatment compliance			X	X	X	X	
EFFICACY ASSESSMENTS							

Procedure	Treatment Period						Notes
Visit	1	2[1]	3	4	5	6	
Day	1	Within 48h / discharge	12	28	56	84	
Visit window	N/A	±1 days	±2 days	±2 days	- 4 / +2 days	- 4 / +2 days	
HRCT (at TLC and FRC)			X	X			At any time on specified days. Includes electronic monitoring of breathing (if applicable). The radiologist may review any of the scan(s) if they wish, but this is NOT required for the study. A formal review is required at screening only by the radiologist.
FEV_1 and FVC	X	X	X	X	X	X	In clinic only for all visits where possible.
PEF	←==========→						Daily before drug administration at home. If subject in hospital, this may be collected using the handheld device provided prior to drug administration.

OTHER ASSESSMENTS							
Blood sample for PK	X		X	X	X	X	Day 1: 5 min and 24 h post-dose. The 24 h post-dose time-point is optional for subjects not hospitalised. Pre-dose at all other time-points.
Sputum induction[3]			X	X		X	
Blood sample for mRNA analysis			X	X		X	
Genetic sample (PGx)[4]		X					Collected at any time after randomisation

1. On discharge if the subject was hospitalized. Within 48 hours of first dose administration if the subject was not hospitalised. See Section 4.2
2. Assessments do not need to be completed if screening assessments conducted within 48 hours
3. Induced sputum collection may be repeated on several occasions if an adequate sample is not produced at the first attempt
4. Informed consent for optional sub-studies (e.g. ,genetics research) must be obtained before collecting a sample. May be obtained at any visits.

7.3. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

If they are being utilised in the study, Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

7.4. Biomarker(s)/Pharmacodynamic Markers

7.4.1. Pharmacodynamic Biomarkers in Sputum

- Collect sputum induction samples at the time-points shown in the time and events table (Section 7.1).
- The sputum induction collection process will follow local standard procedures and guidelines outlined in the SRM.
- The collection of induced sputum may be attempted on several occasions if an adequate sample is not produced at the first attempt.
- Further information on collection, processing, storage and shipping procedures are provided in the SRM.

7.4.2. mRNA in blood

- Collect 2.5 mL of blood into a PAXgene mRNA tube.

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

7.5. Patient diary

The subjects will be provided with a diary to record the following data when at home:

- Time and date of each dose administration and number of inhalations.

- Adverse Events and concomitant medications taken (including daily rescue medication – if used and how many times used).
- PEF from a handheld device. The best/highest result is recorded.

Changes in Health and details of any concomitant medications as well as PEF assessment details will be collected in the paper diaries and later transcribed into the CRF.

7.6. Genetics

Information regarding genetic research is included in Appendix 3.

7.7. Efficacy

7.7.1. Functional Respiratory Imaging

- A CT scan with a low radiation protocol at FRC and TLC will be conducted as listed in the Time and Events Table (Section 7.1). The same scanner should be used for baseline and post-treatment scans for an individual subject.
- A urine pregnancy test should be performed before the CT scan in female subjects of childbearing potential.
- Further information is provided in the SRM.

7.7.2. FEV_1 and FVC

A triplicate FEV_1 and FVC measurement will be taken at the clinic before dosing using the site's spirometer as soon as it is safe to do so. Predicted values will be based upon the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012].

- Further details are provided in the SRM.

7.7.3. Peak Expiratory Flow PEF

- PEF measurements will be taken (in triplicate) daily in the morning before dose administration, as soon as it is safe for the subject to do so. The best/highest result is recorded.
- Subjects will be provided with a handheld device.
- Further details are provided in the SRM.

7.8. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.8.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.8.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.8.1.3), at the time-points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.8.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”

- "Have you had any (other) medical problems since your last visit/contact
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.8.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

7.8.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

7.8.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless they meet the definition of an SAE as defined in Appendix 4 Exacerbations that meet the definition of an SAE will be recorded on the appropriate eCRF section and should be reported to GSK.

Medications used to treat a COPD exacerbation will be recorded in the exacerbation eCRF

7.8.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the

regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.8.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until the follow-up visit
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.8.3. Physical Exams

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

7.8.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.
- Three readings of blood pressure and pulse rate will be taken
- First reading should be rejected
- Second and third readings should be averaged to give the measurement to be recorded in the CRF.

7.8.5. Electrocardiogram (ECG)

- Single 12-lead ECGs will be obtained at screening and at each other timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

7.8.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Historical values (if the assessment was conducted as part of the standard of care) for blood gases, blood culture and sputum culture may also be collected if available.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Table 1 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count		*RBC Indices*:	*WBC count with Differential:*
	RBC Count		MCV	Neutrophils
	Hemoglobin		MCH	Lymphocytes
	Hematocrit			Monocytes
				Eosinophils
				Basophils
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose (non fasted)	Calcium	Alkaline phosphatise	Albumin
	CRP			
Other Screening Tests	• Urine hCG Pregnancy test (as needed for women of child bearing potential) [2] • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody)			

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 5.4.1 and Appendix 2

2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Hematology and clinical chemistry at screening for excluding subjects with severe disease and uncontrolled medical conditions. The results of each test must be entered into the CRF.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

Hematology, clinical chemistry and additional parameters to be tested are listed in Table 1.

7.9. Pharmacokinetics

7.9.1. Blood Sample Collection

A 2 mL blood samples for pharmacokinetic (PK) analysis of GSK2269557 will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.9.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK2269557 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for GSK2269557 any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK/Scinovo, GlaxoSmithKline protocol.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSK Drug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

This study is designed to establish the PI3Kδ-dependent alterations in immune cell mechanisms related to neutrophil function as detected by changes in mRNA transcriptomics in samples of induced sputum from patients admitted with an exacerbation of COPD. The primary comparison will be between subjects treated with GSK2269557 in addition to standard of care, and subjects treated with placebo in addition to standard of care. In addition, treatment comparisons between subjects at baseline and subsequent time points will also be produced.

9.1. Sample Size Considerations

The sample size for this study has been based on feasibility. The sample size of 30 subjects completing the trial, with approximately 15 of which will receive GSK2269557 and 15 will receive placebo, is expected to be sufficient to provide a meaningful estimate of the mRNA alterations within the lungs.

Previous studies with similar sample size populations have yielded significant fold-changes (fold-change>1.5 and $p<0.05$) in immune cell mechanisms using the changes in mRNA transcriptomics.

Study Name	Sample	Study Design	Number of Subjects	Number of Differential probesets FC = >= 1.5, Pval <= 0.05	Notes
PII115117 FTIH Healthy Smoker nebulised GSK2269557	Sputum	Sputum N=12 3-way x-over placebo 400ug, 6400ug	12 (9 with all data points)	57 probesets change with both doses = 44 Genes	Gene changes relate predominantly to a down regulation of infection and inflammation responses. Link to Haemophilus influenzae and Moraxella catarrhalis infection biology – Identified prior to knowledge of Activated PI3Kδ Syndrome phenotype
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Sputum	Ex vivo Sputum incubated with GSK2269557 sampled at 6hrs (Sputum producers)	15 Subjects	490 probesets change vs vehicle control = 295 genes (of which 43 are dysregulated in COPD disease vs Healthy comparison)	43 genes altered in COPD and positively modulated by PI3Kδi GSK2269557. Biological themes in signature: Pro-cell movement/migration and cell viability, anti-apoptotic. Additionally link to B/T cell function. Signature supports GSK2269557 correction of neutrophil migration
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at 6hrs (Sputum	15 Subjects	19 probesets change vs vehicle control = 15 genes	Infection and inflammation associated genes
200114 Enabler GSK2269557 on ex-vivo COPD Sputum and Blood	Blood	Ex vivo blood incubated with GSK2269557 sampled at	15 Subjects	30 probesets change vs vehicle control = 25 genes	Infection and inflammation associated genes

9.1.1. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed in this study.

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Screened	• All subjects who were screened.	• Study Population
All subject	• All randomised subjects who receive at least one dose of the study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Pharmacodynamics • Safety • Efficacy
Pharmacokinetic	• Subjects in the 'All subject' population for whom a pharmacokinetic sample was obtained and analysed.	• PK

9.2.2. Interim Analysis

No interim analyses will be performed.

9.3. Key Elements of Analysis Plan

9.3.1. Primary Analyses

To estimate differences in mRNA intensities within and between treatment groups, a repeated measures model will be fitted to the results of the analysis of each probe set at Day 12, Day 28 and Day 84 following a loge transformation of the data. The Day 1 response will be fitted as a baseline covariate. A separate model will be fitted for each of the approximate 54000 probe sets.

Back transformed ratios versus screening along with 95% confidence intervals will be calculated for each treatment group and timepoint. Additionally, baseline adjusted ratios of the change between active treatment and placebo will be calculated along with 95% confidence intervals.

Further details around the analysis of the mRNA data will be provided in the RAP.

9.3.2. Secondary Analyses

All secondary analyses will be described in full prior to unblinding in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable

- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

AE	Adverse Event
ALT	Alanine aminotransferase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
ECG	Electrocardiogram
FEV1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
GCP	ICH Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
PEF	Peak Expiratory Flow
PI3Kδ	Phosphoinositide 3-Kinase Delta
PK	Pharmacokinetic
QTcF	QT interval corrected using the Fridericia's formula
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SRM	Study Reference Manual
TLC	Total Lung Capacity
ULN	Upper Limit of Normal

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DISKUS

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **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 subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (refer to Appendix 2). • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained 7 days after last dose[5] • 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

treatment and may continue subject in the study for any protocol specified follow up assessments	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form
MONITORING: **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • 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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, 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 subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. 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
5. PK sample may not be required for subjects 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 blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.3. Appendix 3: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- COPD susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to

the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • 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 medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where 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.

12.4.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject 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 out-patient setting. Complications that occur during hospitalization are AEs. 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 disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are 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

g. Is associated with liver injury and impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject'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 instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.

- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of 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 when 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 prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject 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 the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication

Pregnancy information on female partner of male study subjects

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks 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: Country Specific Requirements

No country-specific requirements exist.