TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	An open-label, single arm study to investigate the safety, pharmacokinetics and pharmacodynamics of repeat doses of inhaled nemiralisib in patients with APDS/PASLI

Compound Number: GSK2269557

Development Phase: IIA

Effective Date: 15-JUN-2018

Protocol Amendment Number: 03

Author s: PPD , (Respiratory R&D); PPD (Respiratory R&D); PPD (GCSD),PPD (GCSD); PPD (Clinical Statistics); PPD (Respiratory R&D); PPD (CPMS); PPD (CPMS)

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N238311_00	2015-OCT-23	Original
2015N238311_01	2016-FEB-25	Amendment No. 1

Summary of Protocol Amendment 01 (a detailed description of the amendment is provided in Appendix 6):

1. Minor change to the wording of the exploratory efficacy endpoint has been made.
2. Reference to randomisation of subjects removed for clarity and accuracy.
3. Mitigation strategy of the APDS exacerbation risk has been updated to ensure consistency with the weeks the clinic visits occur on, as described in the protocol
4. Removal of instruction on the need for precautionary measures to protect against potential photosensitive effects of GSK2269557 (following new non-clinical data supporting the discharge of this risk to humans)
5. Maximum weekly alcohol consumption for males reduced from 21 to 14 units. Updated to reflect current UK guideline following the recent change in advice.
6. Additional exclusion criteria added to exclude subjects who provide a positive sample in a pre-study drug screen.
7. Immunoglobulins added to the list of PD lymphocyte assessments to provide further characteristics pertaining to lung infection in APDS patients.
8. Time and Events Table for Screening and Run-in Period updated as follows:
   - Immunoglobulins added to the list of PD lymphocyte assessments
   - Timing of PD sample collection for bacterial DNA fragment analysis added and to ensure consistency with body text.
   - Laboratory tests for clotting status added to clinical visit #1 for subjects consenting to the BAL sub-study.
9. Time and Events Table for Treatment Period and Follow-up updated as follows:
   - Timing of reviews of APDS exacerbation and respiratory tract infection history added to make consistent with body text.
   - Day 2 PK blood sample (which refers to Day 1 24 hr timepoint) removed from table for clarity
   - Immunoglobulins added to the list of PD lymphocyte assessments
   - Timing of PD sample collection for bacterial DNA fragment analysis added to ensure consistency with body text.
   - Laboratory tests for clotting status added to Day 83 (-4/+2) for subjects consenting to the BAL sub-study.
10. Removal of 'severity of infection' as a measurement taken during the

screening and critical baseline assessments 11. Clarification of the period during which details of pregnancies in female subjects will be collected after the start of dosing 12. Addition of two haematology laboratory tests for clotting status to be performed at clinical visit #1 and Day 83 (-4/+2) for subjects consenting to the BAL sub-study. 13. Clinical Chemistry section amended to clarify that blood glucose test is a non-fasting measurement. 14. Additional text added to clarify which lung lobe will be targeted during the BAL procedure. 15. Proposed analyses of BAL updated to indicate that proteomic analysis will be performed on the lavage supernatant *not* the cell pellet. 16. Additional text added to analysis section to clarify the timing of reporting of exploratory biomarker data to ensure publication of data pertaining to core primary and secondary measures is not delayed.		
2015N238311_02	2016-NOV-02	Amendment No. 2
Summary of Protocol Amendment 02 (a detailed description of the amendment is provided in Appendix 6): 1. Replace the administration of GSK2269557 via the DISKUS device (1000 μg) by a comparable dose administered via the ELLIPTA device (700 μg) 2. Include patients with APDS1 with new disease-associated mutations and APDS2 with mutations in the PIK3R1 regulatory subunit of class IA phosphoinositide 3 kinases. 3. Administrative changes and clarifications.		
2015N238311_03	2018-JUN-15	Amendment No. 3
Summary of Protocol Amendment 03 (a detailed description of the amendment is provided in Appendix 6): 1. Replace the administration of nemiralisib in a blend containing 0.6% MgSt, via a dry powder ELLIPTA inhaler (700 μg) by a comparable dose nemiralisib in a blend containing 0.4% magnesium stearate (MgSt) administered via the ELLIPTA device (500 μg). 2. Exploratory Phamacodynamics endpoint Volatile Organic Chemicals (VOCs) analysis in breath removed as capabilities not available at study site. 3. Risk assessment table updated with post inhalation cough. 4. Change to inclusion criteria 3 the lower limit BMI cut off to 17 kg/m2 and the		

lower limit for weight to 40kg. These patients have a longstanding chronic condition and so are more likely to fall outside the normal range for BMI. Therefore adoption of a slightly lower BMI for this patient group is considered appropriate and safe.

5. Change to inclusion criteria 4. Based on the predicted margins for semen exposure on findings across the reproductive toxicology studies range between 29811 and 192452 fold, which are well above the threshold for concern, and the absence of genotoxic effects in cellular assays, the requirement for additional contraception for males with partners of child bearing potential has been removed.

6. Change to exclusion criteria 5 concomitant medication. Adjusted in line with latest drug interaction data. Information about interaction with inhibitors of CYP3A4 substrates has been added for consistency since this has also been implemented for the most recent studies.

7. Dose reduction removed as dose strength is 500µg / blister, therefore dose reduction will no longer be an option.

8. Time and Event schedule visit window added to Follow Up Visit.

9. Administrative changes, including change from the compound number GSK2269557 to the INN nemiralisib, corrections, relevant updates, including reporting time frame of pregnancy information and clarifications also made.

SPONSOR SIGNATORY

PPD

15th June 2018

Anthony Cahn
Head Respiratory TAU & Flexible Discovery Unit
GlaxoSmithKline

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): **2015-004876-31.**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204745

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 204745

Rationale

The purpose of this study is to investigate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) during 84 days treatment with 500 μg of inhaled nemiralisib in addition to standard of care, in patients with activated phosphoinositide 3-kinase delta syndrome 1/p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (APDS1/PASLI-CD) and activated phosphoinositide 3-kinase delta syndrome 2/p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (APDS2/PASLI-R1).

To date nemiralisib has been administered to healthy subjects (smokers and non-smokers), patients with: stable Chronic Obstructive Pulmonary Disease (COPD); patients experiencing a COPD exacerbation; and patients with persistent, uncontrolled asthma. As this study is the first administration of nemiralisib to patients with APDS, this study will provide safety, tolerability, efficacy and pharmacokinetic data in this patient population.

The study will also explore the pharmacodynamic effects of once daily (OD) repeat inhaled doses of nemiralisib administered to APDS patients on biomarkers in blood and sputum. In a sub-study, subjects will undergo bronchoalveolar lavage (BAL) to investigate lymphocyte biology in the lungs after dosing with nemiralisib.

Objectives/Endpoints

Objectives	Endpoints
Primary	
Safety To assess the safety and tolerability of 84 days repeat dosing of inhaled nemiralisib in patients with APDS	• Adverse Events (AE) • Vital signs • 12-lead electrocardiogram (ECG) • Clinical laboratory parameters, • Spirometry (forced expiratory volume in 1 second (FEV1) 1 hr post-dose)
Secondary	
Pharmacokinetics To define the plasma pharmacokinetics (PK) of inhaled nemiralisib following repeat dosing in patients with APDS.	Nemiralisib trough plasma concentration following single and repeated treatment.
Exploratory	
Pharmacodynamics: To understand lung disease biology in patients with APDS and to explore the pharmacodynamic effects of inhaled nemiralisib.	Endpoints may include, but are not limited to: ***In blood and sputum, analysis of:*** • Cellular PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area) • Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) • Immune cell subsets

Objectives	Endpoints
	• Exploratory phospho-protein biomarkers (e.g. pAKT) • Exploratory messenger ribonucleic acid (mRNA) biomarkers ***In BAL cell pellet/*** **lavage supernatant** ***when available, analysis of:*** • Lymphocyte cell subsets • Exploratory phospho-protein biomarkers (e.g. pAKT) • Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) • Exploratory mRNA biomarkers • Proteomic markers (lavage supernatant only) • Antibody levels ***In blood, analysis of:*** • Bacterial DNA fragments
Pharmacokinetics To define the lung trough concentration of nemiralisib after repeat dosing	Trough nemiralisib concentration in lung epithelial lining fluid (ELF) and bronchoalveolar lavage (BAL) cell pellet at Day 84 visit.
Efficacy To assess the efficacy of inhaled nemiralisib administered once daily for 84 days in patients with APDS.	• The number and rate of pulmonary and/or ear and sinus infections requiring anti-microbial treatment compared to subject's historical baseline • Change from baseline (Day 1) in trough FEV1at Day 14 and Day 83 (pre-bronchodilator)

Overall Design

This is a single-centre, open-label, uncontrolled, single group, study in patients with APDS 1 and 2.

- Eligible subjects will be enrolled in the study and receive nemiralisib 500 μg once daily for 83 days (-4/+2 days).
- Nemiralisib will be administered via the ELLIPTA™ Dry Powder Inhaler (DPI).
- In an optional sub-study, subjects will undergo bronchoalveolar lavage (BAL) to investigate lymphocyte biology in the lungs after dosing with nemiralisib for 84 days (-4/+2 days).

Treatment Arms and Duration

Subjects will be required to participate in the following visits:

Pre-screening: subjects will visit the study clinic to sign the Informed Consent Form and undergo review of demography, APDS exacerbation history and concomitant medications. Any medication changes made by the investigator will be recorded.

Screening: Subjects will visit the study clinic for an assessment of eligibility criteria up to 42 days before the treatment period (Day -1). Subjects meeting the eligibility criteria, which can be assessed at the screening visit, will visit the study clinic up to 7 days before first dose to complete the baseline assessments.

Note: Pre-screening and screening visits may occur on the same day, as appropriate.

PD Baseline assessment (Visit #1): Subjects will undergo a range of baseline assessments described in the Time & Event table, including providing a sample of blood and induced sputum.

Optional BAL sub-study*:* subjects willing to participate in the BAL sub-study will undergo a bronchoscopy/BAL baseline assessment (BAL visit #1). This may occur *either* on day 2 of the PD baseline assessment *or* during a separate visit, as appropriate.

Treatment Period: Once daily treatment of nemiralisib will start on Day 1.

- Subjects will visit the study clinic the day before dosing (Day -1) and undergo a range of baseline assessments described in the Time & Event table.
- Once daily study treatment administration will start on Day 1. Subjects will remain in the study clinic until all the safety assessments have been completed on Day 2, and there are no safety concerns.
- Subjects will then dose at home for the remainder of the treatment period (with the exception of clinic visit days, when they will dose in the study clinic). On Day 14 ± 2, Day 28 (-4/+2 days), Day 56 (-4/+2 days), Day 83 (-4/+2 days) and Day 84 (-4/+2 days) (optional sub-study patients only), subjects will return to the study clinic on an outpatient basis, in order to complete the assessments described in the Time & Event table.
- Between Day 2 and Day 84, subjects will be contacted weekly by telephone or a research nurse will visit them at home, to ensure there are no safety concerns. During this period subjects will be encouraged to contact the study clinic immediately upon the worsening of any symptoms.

Follow up period:

- Subjects will receive telephone calls at 1-2 weeks and 4-6 weeks after their last dose. These will be used to ensure there are no safety concerns and to monitor the number and rate of lower/upper respiratory tract infections requiring antimicrobial therapy.
- Three months after the end of treatment, subjects will return to the study clinic to perform a range of follow-up assessments, described in the Time & Event table.

The total duration of the study is approximately 30 weeks, including pre-screening/screening and follow-up.

Type and Number of Subjects

Patients with Documented Type 1 or 2 APDS/PASLI-associated genetic PI3Kδ mutation (e.g. E1021K, N334K, E525K and C416R)

- Up to 20 subjects will be enrolled into the study with the aim to ensure approximately 4 subjects complete dosing and critical assessments.

Analysis

Safety data will be graphically presented, summarised and listed as appropriate. Data permitting, the pharmacodynamic endpoints will also be summarised, and may be analysed if deemed appropriate.

2. INTRODUCTION

Nemiralisib is a potent and highly selective inhaled PI3Kδ inhibitor being developed as an agent for the treatment of inflammatory airways diseases.

2.1. Study Rationale

The purpose of this study is to investigate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) during 84 days treatment with 500 μg of inhaled nemiralisib in addition to standard of care, in patients with activated phosphoinositide 3-kinase delta syndrome 1/p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (APDS1/PASLI-CD) and activated phosphoinositide 3-kinase delta syndrome 2/p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (APDS2/PASLI-R1).

To date nemiralisib has been administered to healthy subjects (smokers and non-smokers), patients with stable Chronic Obstructive Pulmonary Disease (COPD), patients experiencing a COPD exacerbation and patients with persistent, uncontrolled asthma. As this study is the first administration of nemiralisib to patients with APDS, this study will provide safety, tolerability, efficacy and pharmacokinetic data in this patient population.

The study will also explore the pharmacodynamic effects of once daily repeat inhaled doses of nemiralisib administered to APDS patients on biomarkers in blood and sputum.

In a sub-study, subjects will undergo bronchoalveolar lavage (BAL) to investigate lymphocyte biology in the lungs after dosing with nemiralisib.

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].
APDS1 (PASLI-CD) is a rare (prevalence estimated to be <1/1,000,000), combined primary immune deficiency syndrome caused by a dominant gain-of-function heterozygous mutation in p110δ, the catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ). A number of mutations e.g. E1021K, N334K, E525K and C416R, with E1021K the most common [Angulo, 2013; Lucas, 2014] have been described. Clinically, APDS is characterized by recurrent respiratory infections with *Streptococcus pneumoniae* and *Haemophilus influenzae*, causing structural lung damage (small airways disease and bronchiectasis). In addition, some patients experience severe infections with Herpes-group viruses, and there is an increased risk of B cell malignancy [Lear, 2014]. Typically, disease in APDS patients is difficult to manage, with the use of prophylactic antibiotic and antiviral agents, i.v. antibiotics, and immunoglobulin replacement being the mainstay of treatment. The limited treatment options available to these patients' means early death from infection-related causes remains a prominent feature of the disease [Lear, 2014]. Recently, APDS 2 (PASLI-R1), a primary immunodeficiency resulting from autosomal dominant gain-of-function mutations in PI3KR1, the gene coding for the regulatory subunit of class PI3Ks, has been described. The clinical, immunological and histopathological features of APDS2 are similar to those described in APDS1 patients [Elkaim, 2016, Olbrich, 2016].

Immunologically, these patients have increased transitional but decreased memory B cells, circulating senescent T cells, increased IgM but reduced IgG2 levels, and impaired vaccine responses [Angulo, 2013; Lucas, 2014] . In vitro the E1021K mutation enhanced the membrane association and kinase activity of p110δ. Biochemically, patient-derived lymphocytes displayed increased basal and stimulated phospho-AKT and PIP3 (the second messenger product of PI3K), a propensity for activation induced cell death (AICD) and impaired cytokine production. Importantly, selective PI3Kδ inhibitors IC87114 and GS-1101 (CAL-101, idelalisib) reduced activity of the mutant kinase *in vitro* and in patient T cells *ex vivo*, and prevented AICD, suggesting a novel, target-specific therapy for APDS [Angulo, 2013].

Nemiralisib is a potent and highly selective inhaled PI3Kδ inhibitor and therefore has the potential to be a novel therapy in patients with APDS.

Nemiralisib has been administered to healthy volunteers and healthy smokers in previous studies, as follows:

- *Study PII115117 (healthy volunteers):* single and repeat doses of a nebulised solution of nemiralisib – daily doses up to 6400 µg for 7 days.
- *Study PII116617 (healthy smokers):* single and repeat doses of a dry powder formulation (DISKUS™ dry powder inhaler; DPI) of nemiralisib – single doses up to 3000 µg, and daily doses up to 2000 µg for 14 days
- *Study 201544 (healthy volunteers):* single centre, three part, randomised, study to evaluate the safety, tolerability and pharmacokinetics of nemiralisib administered via the ELLIPTA™ dry powder inhaler (0.6% MgSt formulation) – single doses up to 200 µg, and daily doses of 200 µg for 10 days.
- Study 205759 (*healthy Japanese volunteers*): single and repeat doses of nemiralisib administered via the ELLIPTA™ DPI (0.6% MgSt formulation) – single doses up to 700 µg, and daily doses up to 700 µg for 10 days.
- Study 207674 (*healthy volunteers*): single dose of nemiralisib 750 µg or a single dose of 500 µg administered via the ELLIPTA™ DPI (0.4% MgSt formulation) (study completed but not yet reported).
- Study 206764 (*healthy volunteers*): An open-label study in healthy male subjects, to determine the excretion balance and pharmacokinetics of [14C]-GSK2269557, administered as a single intravenous micro-tracer (concomitant with an inhaled non-radiolabelled dose) and a single oral dose (study completed but not yet reported).
- Study 206874 (*healthy volunteers*): one sequence cross over study (nemiralisib 100 µg (via the ELLIPTA™ DPI (0.4% MgSt formulation) alone followed by nemiralisib 100 µg co-administered with itraconazole). A study to evaluate the effect of itraconazole on the PK of nemiralisib (study completed but not yet reported)

Nemiralisib was well tolerated across the range of doses tested.
Nemiralisib has been administered to COPD patients in the following studies:

- *Study PII115119 (stable COPD patients):* daily doses of up to 2000 µg nemiralisib administered via the DISKUS™ DPI for 14 days.
- Study PII116678 (patients experiencing a COPD exacerbation): daily doses of 1000 µg nemiralisib administered via the DISKUS™ DPI for 12 weeks.

Nemiralisib has been administered to patients with persistent, uncontrolled asthma:

- Study 201543 (*patients with persistent, uncontrolled asthma*): daily doses of 1000 µg nemiralisib are being administered via the DISKUS™ DPI for 28 days

There are also two ongoing studies (not reported) in COPD patients:

- *Study 201928 (patients experiencing a COPD exacerbation):* daily doses of 700 µg nemiralisib being administered via the ELLIPTA™ DPI (0.6% MgSt formulation) for 12 weeks.

- Study 200879 (*patients experiencing an acute COPD exacerbation*): daily doses up to 750µg nemiralisib administered via the ELLIPTA™ DPI (0.4% MgSt formulation) for 84 days in a dose ranging study.

More information about the non-clinical and clinical studies is available in the investigator's brochure (IB) [GlaxoSmithKline Document Number 2012N141231_08].

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
Safety To assess the safety and tolerability of 84 days repeat dosing of inhaled nemiralisib in patients with APDS	• Adverse Events (AE) • Vital signs • 12-lead electrocardiogram (ECG) • Clinical laboratory parameters, • Spirometry (forced expiratory volume in 1 second (FEV1)1 hr post-dose)
Secondary	
Pharmacokinetics To define the plasma pharmacokinetics (PK) of inhaled nemiralisib following repeat dosing in patients with APDS.	Nemiralisib trough plasma concentration following single and repeated treatment.
Exploratory	
Pharmacodynamics: To understand lung disease biology in patients with APDS and to explore the pharmacodynamic effects of inhaled nemiralisib.	Endpoints may include, but are not limited to: ***In blood and sputum, analysis of:*** • Cellular PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area) • Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) • Immune cell subsets • Exploratory phospho-protein biomarkers (e.g. pAKT) • Exploratory messenger ribonucleic acid (mRNA) biomarkers ***In BAL cell pellet/lavage supernatant when available, analysis of:*** • Lymphocyte cell subsets • Exploratory phospho-protein biomarkers (e.g. pAKT) • Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) • Exploratory mRNA biomarkers • Proteomic markers (lavage supernatant only) • Antibody levels

Objectives	Endpoints
	In blood, analysis of: • Bacterial DNA fragments
Pharmacokinetics To define the lung trough concentration of nemiralisib after repeat dosing	Trough nemiralisib concentration in lung epithelial lining fluid (ELF) and Bronchoalveolar lavage (BAL) cell pellet at Day 84 visit.
Efficacy To assess the efficacy of inhaled nemiralisib administered once daily for 84 days in patients with APDS.	• The number and rate of pulmonary and/or ear and sinus infections requiring anti-microbial treatment compared to subject's historical baseline • Change from baseline (Day 1) in trough FEV1 at Day 14 and Day 83 (pre-bronchodilator)

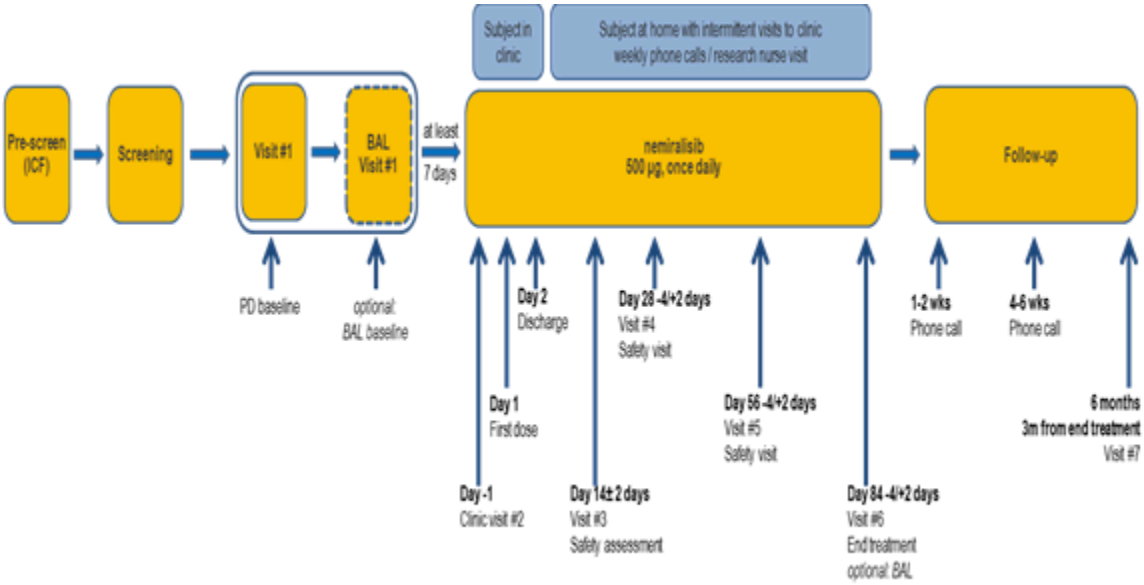
4. STUDY DESIGN

4.1. Overall Design

This is a single-centre, open-label, uncontrolled single group study in patients with APDS 1 and 2.

- Eligible subjects will enter the study and receive nemiralisib 500 μg once daily for up to 83 days (-4/+2 days).
- Nemiralisib will be administered via the ELLIPTA Dry Powder Inhaler (DPI).
- In an optional sub-study, subjects will undergo bronchoalveolar lavage (BAL) to investigate lymphocyte biology in the lungs after dosing with nemiralisib for 84 days (-4/+2 days).

Figure 1 Study Design Schematic



4.2. Treatment Arms and Duration

Subjects will be required to participate in the following visits:
Pre-screening: Subjects will visit the study clinic for signing the Informed Consent Form and undergo review of demography, APDS exacerbation history and concomitant medications. Any medication changes made by the investigator will be recorded.

Screening: Subjects will visit the study clinic for an assessment of eligibility criteria up to 42 days before the treatment period (Day -1). Subjects meeting the eligibility criteria, which can be assessed at the screening visit, will visit the study clinic up to 7 days before first dose to complete the baseline assessments.

Note: Pre-screening and screening visits may occur on the same day, as appropriate.

PD Baseline assessment (Visit #1): Subjects will undergo a range of baseline assessments described in the Time & Event table (Section 7.1), including providing a sample of blood and induced sputum.

Optional BAL sub-study*:* Subjects willing to participate in the BAL sub-study will undergo a bronchoscopy/BAL baseline assessment (BAL visit #1). This may occur *either* on day 2 of the PD baseline assessment *or* during a separate visit, as appropriate.

Treatment Period: Once daily treatment of nemiralisib will start on Day 1.

- Subjects will visit the study clinic the day before dosing (Day -1) and undergo a range of baseline assessments described in the Time & Event table (Section 7.1).
- Once daily study treatment administration will start on Day 1. Subjects will remain in the study clinic until all the safety assessments have been completed on Day 2, and there are no safety concerns.

- Subjects will then dose at home for the remainder of the treatment period (with the exception of clinic visit days, when they will dose in the study clinic). On Day 14 ± 2, Day 28 (-4/+2 days), Day 56 (-4/+2 days), Day 83 (-4/+2 days) and Day 84 (-4/+2 days) (optional sub-study patients only), subjects will return to the study clinic on an outpatient basis, in order to complete the assessments described in the Time & Event table (Section 7.1).
- Between Day 2 and Day 84, subjects will be contacted weekly by telephone or a research nurse will visit them at home, to ensure there are no safety concerns. During this period subjects will be encouraged to contact the study clinic immediately upon the worsening of any symptoms.

Follow up period:

- Subjects will receive telephone calls at 1-2 weeks and 4-6 weeks after their last dose. These will be used to ensure there are no safety concerns and to monitor the number and rate of lower/upper respiratory tract infections requiring antimicrobial therapy.
- Three months after the end of treatment, subjects will return to the study clinic to perform a range of follow-up assessments, described in the Time & Event table (Section 7.1).

The total duration of the study is approximately 30 weeks, including pre-screening/screening and follow-up.

4.3. Type and Number of Subjects

Patients with Documented type 1 APDS/PASLI-associated genetic PI3Kδ mutation (i.e. E1021K, N334K, E525K and C416R)

Up to 20 subjects will be enrolled into the study with the aim to ensure approximately 4 subjects complete dosing and critical assessments.

4.4. Design Justification

This single arm exploratory study is designed to provide initial information on the mechanism of disease including airway biology in this rare APDS patient population, and to identify any initial safety and tolerability issues following 12-weeks dosing with 500 μg nemiralisib. The data collected in this study will be used to inform the design of more expansive studies with nemiralisib in this disease in the future.

Single arm (no placebo)	Given the rareness of this disease and the limited number of eligible subjects, a placebo control was not included. This maximises the number of subjects on-drug and thereby offers an opportunity to better understand the pharmacodynamic effect of the drug in this disease.
Treatment period	• **Safety:** The safety aim of this study is to assess any frequent, safety events which deviate from prior safety data. The 12-week treatment period builds on significant prior data collected in

	healthy volunteers, COPD and asthma patients where nemiralisib has been well tolerated up to 12 weeks treatment. No drug-related serious adverse event(s) (SAEs) have been observed to date. The most common AEs to date are post-inhalation cough and headache. • **PK:** Nemiralisib reaches steady state after 5-7 days repeat dosing. Assessing plasma PK at day 14 & 83 will enable the assessment of a sustained level of nemiralisib exposure in this patient cohort. • **PD:** Changes in a range of PD markers have been measured during studies in patients with COPD, following 2 weeks dosing with nemiralisib.
Endpoint measurements	• The study has been designed to be rich in pharmacodynamic biomarkers to support the evaluation of airway biology in patients with APDS, and the effect of nemiralisib (administered directly to the lung) on the disease. These are assessed from blood, sputum and BAL (where available) samples. • While there is a strong genetic association between the mechanism of disease in APDS and drug action, and there is *in-vitro* peripheral lymphocyte data to support the use of PI3K delta inhibitors in APDS (discussed in Section 2.2), there is no airway-specific *in-vitro* or *in-vivo* data from patients with APDS
Frequency of clinic visits	• Subjects in this study will be monitored more closely than they would be in clinical practice with clinic visits after 14, 28, 56 and 83 days of dosing, and weekly telephone contact or visit by a research nurse. The frequency of the visits will allow for the early identification of deteriorating disease and appropriate diagnostic evaluation and management of subjects. • Subject safety will also be assured by the application of strict withdrawal criteria in the event of deterioration of the subjects' condition.
Pre-screening visit	Inclusion of a pre-screening visit will enable the assessment of subjects' concomitant medications ahead of screening. This allows time ahead of dosing, if changes are required, to ensure patients are stable on alternative medications
Pre-treatment baseline visits	To mitigate against the inclusion of a placebo control, we are taking two sets of pharmacodynamic samples prior to dosing to obtain a more robust baseline measurements.
Follow-up period and clinic visit	• The inclusion of a 3-month follow-up period will enable the tracking of sinus, ear and pulmonary infection rate post-drug. This will control for the seasonality of infection frequency, which is important for the efficacy endpoint. • The measurement of PD markers at the 3 month follow-up period will enable us to obtain more robust baseline measurements

4.5. Dose Justification

The formulation of Nemiralisib has been changed to the current formulation of nemiralisib with lactose monohydrate/0.4% Magnesium Stearate (MgSt) which is the proposed final formulation and currently being investigated in the dose ranging study. The previous formulation currently used in the study is blended with lactose and 0.6% MgSt). The reduction in concentration of MgSt in the new formulation has resulted in a change in the respirable mass of the drug product and hence a reduction in dose is possible. The blend containing 0.4% MgSt is considered the final formulation and intended for progression into Phase III and favours a lower total doses of drug for further development.

The dose chosen for this study is 500 µg of nemiralisib per day administered via a dry powder ELLIPTA inhaler containing 0.4% MgSt for a duration of up to 84 days (-4/+2 days) and is expected to be equivalent to a dose of either 700 µg nemiralisib blended with 0.6% MgSt administered via the ELLIPTA DPI or the 1000 µg administered via DISKUS in terms of the dose deposited and retained within the lungs based on PK parameters (AUC and C_{max}). The delivered dose and deposition profile to the lungs is a function of the device and formulation which is reflected in the observed data (plasma pharmacokinetics) for all the formulations. Data and plasma exposures have been generated (completed or ongoing studies) in human for these different devices and formulations (up to 2000 µg in DISKUS once daily for 14 days in PII116617; 700 µg in ELLIPTA DPI (0.6% MgSt formulation) once daily for 10 days in 205759 and 750 µg in ELLIPTA DPI (0.4% MgSt formulation) once daily for 3 months in the ongoing 2b study 200879 in exacerbating COPD patients). A recent healthy volunteer trial using the ELLIPTA DPI 0.4% MgSt formulation has been compared (using plasma exposure following 500 µg) with the data generated for each device and formulation in terms of the observed trough (24 hours post dose) concentrations and these are shown in the following table.

Table 1 Observed plasma concentrations on Day 1 at trough (24 hours post dose) in healthy volunteers following inhaled Nemiralisib administration by device/material

Study	Device/Material	Population	Dose (µg)	Plasma Ctrough (24 hrs post Day 1 dose) pg/mL	
				Geometric mean	95% CI
PII116617	DISKUS	HVT	1000*	196	167-230
205759	ELLIPTA DPI 0.6%MgSt	HVT - Japanese	700	239	180-316
207674^	ELLIPTA DPI 0.4%MgSt	HVT	500	166	120-228

* Extrapolated from 2000 µg (Ctrough at 24h of 392 pg/mL and 90% confidence interval of 334-460) dose level since 1000 µg was not a dose level in study PII116617

^ Preliminary data from a completed but unreported trial 207674

The selected 500 ug dose is expected to achieve a similar level of inhibition of PI3Kδ within the lungs during the treatment phase of this study on a once a day regimen as the 700 µg administered via ELLIPTA DPI (0.6% MgSt formulation) or 1000 µg

administered via DISKUS. This dose has been selected based on previous safety and tolerability data in humans including healthy subjects, healthy smokers and COPD patients including exacerbating patients following nemiralisib administration via a DISKUS DPI, and healthy subjects via ELLIPTA DPI, as well as pharmacokinetics and demonstration of target (PI3Kδ) inhibition by observed changes in biomarkers. This will be the first time nemiralisib is dosed to patients who have been identified as having APDS, and it is assumed that these patients will have a similar lung deposition, distribution and plasma exposure to healthy volunteers and COPD patients. No differences between populations of healthy volunteers and patient groups has been observed in inhaled systemic plasma exposure parameters in studies to date.

The nature of the mutation in APDS 1 and 2 patients causes a modification in the catalytic and regulatory subunits of PI3Kδ respectively leading to a lower activation threshold of the enzyme and hence a faster rate of PIP_2 conversion, higher levels of PIP_3, and by implication, localised immune-suppression and a predisposition to infection and subsequent tissue damage [Angulo, 2013, Elkaim, 2016]. Nemiralisib is a competitive antagonist preventing ATP driven PIP_2 conversion and is therefore expected to achieve similar levels of PI3Kδ enzyme inhibition in APDS patients to those seen in healthy subjects, but lead to an overall greater reduction in PIP_3.

The target site of action for inhaled PI3Kδ inhibition is the intracellular compartment of immune cells resident in lung tissue and lumen. Nemiralisib has a high potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL). The pathophysiology of APDS is not fully understood, but is believed to involve a significant neutrophil component as well as T/B-cell and leukocyte driven effects. The predicted steady-state intracellular concentration of nemiralisib at trough (24h) in the lungs of APDS patients is approximately 156 ng/mL (3.3 ng/mL free drug) following 500 µg ELLIPTA DPI 0.4% MgSt formulation, implying PI3Kδ inhibition in excess of 80% throughout the dosing interval in all cell types of interest. Systemic exposure and tissue concentrations are predicted to be extremely low (Cmax of 4.5 ng/mL, 0.09 ng/mL free drug), implying very little PI3Kδ inhibition outside of the lung.

Pharmacodynamic assessments conducted during the trial will monitor target engagement and downstream effects to be measured with a view to confirming the PKPD relationships in these APDS patients.

Any patient participating in this study prior to approval of the protocol supporting the switch to the ELLIPTA DPI (0.4% MgSt) will complete the study with the ELLIPTA DPI (0.6% MgSt). Patients enrolled after approval of the ELLIPTA device (0.4% MgSt) will start and complete the study with the ELLIPTA DPI (0.4% MgSt).

4.6. Benefit:Risk Assessment

4.6.1. Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with nemiralisib can be found in the Investigator's Brochure [GlaxoSmithKline Document

Number 2012N141231_08]. The following section outlines the risk assessment and mitigation strategy for this protocol.

GlaxoSmithKline (GSK) has assessed this study for any potential risks that a subject may experience. The investigational medicinal product nemiralisib has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported by the results of previously conducted and currently ongoing clinical studies with nemiralisib in healthy subjects, patients with COPD and patients with asthma.

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., nemiralisib]		
Paradoxical bronchospasm that may be life-threatening	Known effect associated with inhaled treatment	Treat immediately with a short-acting inhaled bronchodilator. Nemiralisib should be discontinued immediately, the subject assessed and, if necessary, an alternative therapy instituted as deemed appropriate by the investigator or the attending physician. Subjects will be withdrawn from the study.
Mucosal irritancy	Preclinical toxicology findings	Not observed in clinical studies to date. Carefully monitor subjects (AEs, lung function – spirometry).
Post-inhalation cough immediately following inhalation of study treatment (nemiralisib)	In the Proof-of-Concept (PoC) study PII116678, which was conducted in 126 randomized participants from a population similar to this protocol and a previous formulation of nemiralisib (DISKUS formulation blended with only one excipient, lactose), there was a higher incidence of treatment-related, mild and moderate adverse events of cough (Preferred Term) reported immediately after dosing in exacerbating subjects in the nemiralisib DISKUS 1000 mcg QD group (n=22 [35%] compared exacerbating subjects in the placebo DISKUS group (n=2 [3%]). For the 22	The ICF will inform participants that in previous clinical trials, post-inhalation cough has been reported following nemiralisib administration and that the post-inhalation cough is considered related to nemiralisib. In addition, participants will be able to record any AE's (including events of post-inhalation cough) in the diary card provided (See Section 7.8).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	subjects in the nemiralisib 1000 mcg group, the events for 20 of the subjects were considered by the Investigator to be related to study treatment. From the review of reported terms, cough often occurred immediately after dosing and in some subjects it seemed to repeat on most of the dosing days. Cough was reported to be generally mild or moderate and resolved after stopping dosing. Three subjects (all in the nemiralisib DISKUS 1000 mcg QD group) discontinued the study due to cough. Additional details are provided in the Nemiralisib (GSK2269557) Investigator's Brochure.	
APDS exacerbation An exacerbation of APDS is defined as a culture-documented or suspected bacterial, viral or fungal infection, either organ-specific (local) or systemic, which requires antimicrobial treatment or leads to a change in APDS management. This could include emergency room treatment or	Common risk for this patient population is the occurrence of recurrent episodes of infections (these may vary in severity and be bacterial or viral in nature) affecting a number of different organs (e.g. ear, lung). Some of these infections may be systemic.	• Subjects will visit the study clinic frequently (week 2, 4, 8 and 12) and will be monitored remotely by phone in-between these clinic visits. Furthermore subjects will be taking nemiralisib in addition to their standard of care and will be monitored by qualified investigators for any AE/SAE/exacerbation. • In the event of a suspected exacerbation, the subject will undergo an appropriate diagnostic and clinical work-up, with treatment including,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
hospitalization.		but not limited to, antimicrobial treatment instituted as needed by the investigator or attending physician. Treatment should take local guidelines, especially on local antimicrobial resistance, into consideration.
Hypersensitivity to lactose	Lactose is an excipient in the investigational product formulation	Subjects with milk protein allergy or known hypersensitivity to lactose or any other ingredient of the preparation will be excluded from participating in the study.
Unknown risks to an embryo, fetus or nursing infant	There are no studies with nemiralisib in pregnant or lactating women.	As specified in the protocol: • Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate. Female subjects must be postmenopausal or using a highly effective contraception method to avoid pregnancy while in this study. • If a female subject becomes pregnant during the study, she must let the study doctor know immediately. The study medication will be stopped. • For women of reproductive potential, a pregnancy test will be performed at Screening, on Day 1 and Day 28 and at the Follow-up Visit.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Spirometry procedures	Shortness of breath, coughing, light headedness or fainting, and/or chest tightness	If any of these symptoms occur, spirometry will be stopped and the subject will receive medical treatment.
Sputum induction	Bronchoconstriction may occur following inhalation of saline	• Subjects will receive a bronchodilator prior to sputum induction • Sputum induction will be performed and monitored by suitably trained medical staff. • The procedure must be stopped immediately and the subject treated with a short-acting inhaled bronchodilator or other appropriate treatment will be administered deemed by the Investigator or the attending physician.
Bronchoscopy and BAL	Sore throat, haemoptysis and pneumothorax may occur 24-48 hours after the procedure There is also a small risk of transient pyrexia that typically occurs within 24-48-hours of the BAL procedure.	• Bronchoscopy/BAL will be performed by an experienced bronchoscopist in accordance with the guidelines published by the British Thoracic Society, 2013 [Du Rand, 2013] in a dedicated endoscopy area. • The use of sedation and local anaesthetics for the bronchoscopy will be closely controlled and subjects will be pre-medicated with bronchodilator and will be continuously monitored throughout the procedure. The procedure is therefore considered low risk • In case of an adverse event following the BAL

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		procedure (subjects will be informed of the symptoms that may signify infection or pneumothorax), subjects will be admitted to the unit/hospital for observation at the discretion of the investigator (if this occurs before discharge from the endoscopy unit) or asked to return in case symptoms occur after discharge, and will be managed accordingly.

4.6.2. Benefit Assessment

The following are key benefits:

- All subjects will undergo a thorough medical assessment during the study. Subjects will have frequent study clinic visit and telephone calls for the evaluation of their disease symptoms. During these visits, subjects will have spirometry tests, ECG, vital signs monitoring, and physical examinations. Monitoring for worsening of their disease will also take place.
- Subjects may benefit from the knowledge that they are contributing to the process of developing a new treatment in an area of unmet need, even if not directly beneficial for them
- All subjects will continue (with changes, where needed, to antimicrobial treatment that are not strong cytochrome (CYP)3A4 inhibitors) to receive established standard of care

4.6.3. Overall Benefit: Risk Conclusion

Taking into account the measures to minimise risk to subjects, the potential risks associated with nemiralisib and the study procedures, are considered to be minimal and justified by the anticipated benefits that may be afforded to patients with APDS who have no other treatment options.

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/IB supplement(s).

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:

AGE
1. Male and female subjects aged 18 or older at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Patients with a clinical phenotype consistent with APDS, including a history of recurrent (frequency greater than would be expected in an immunocompetent

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
individual) ear, sinus or pulmonary infections, and who have a known type 1 APDS-associated genetic PI3Kδ mutation (e.g. E1021K, N334K, E525K and C416R) or type 2 APDS-associated mutation

WEIGHT
3. Body weight ≥40 kg and body mass index (BMI) ≥17 kg/m^2 (inclusive)

SEX
4. **Female subject.** A 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: • Non-reproductive potential defined as: o 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 o Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. • Reproductive potential and agrees to follow one of the options listed in the-Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of-Reproductive Potential (FRP) (see Appendix 5) from 30 days prior to the first-dose of study medication and until completion of the follow-up telephone call at-1-2 weeks from last dose. • The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
5. 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:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Alanine aminotransferase (ALT) >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 2. Current or chronic history of liver disease except where hepatomegaly is identified by their clinician to be secondary to APDS, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 3. QTc > 450 millisecond (msec) or QTc > 480 msec in subjects with Bundle Branch Block NOTES: • The QTc is the QT interval corrected for heart rate (HR) according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. • The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. • For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP). 4. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator, in consultation with the Medical Monitor if required, agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

CONCOMITANT MEDICATIONS
5. **CYTOCHROME P450 3A4:** **Strong CYP3A4 substrates:** Strong inhibitors of cytochrome P450 3A4: Currently, only limited in vivo information is available on the in vivo metabolism of nemiralisib; and, the role of cytochrome P450s (CYPs) in the elimination of nemiralisib is based upon in vitro data. In vitro studies indicate that nemiralisib is predominantly metabolised by

CYP3A4 enzymes with minor contributions from CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2J2. Co-administration of nemiralisib with CYP3A4 inhibitors may result in increased systemic exposure to nemiralisib. Regular or chronic treatment with medications that are considered strong inhibitors of CYP3A4 are not permitted:

- Antiretrovirals including protease inhibitors (e.g., indinavir, nelfinavir,ritonavir, saquinavir, atazanavir)
- Oral antifungal treatments such as ketoconazole and itraconazole. Short courses of up to 14 days are allowed for fluconazole and voriconazole,but chronic administrations are not permitted. It is recommended that amphotericin or posaconazole are used as oral antifungal treatment of choice.
- Antibiotics such as telithromycin and troleandomycin (macrolide). Short courses up to 14 days are allowed for mibefradil (calcium channel blocker), erythromycin and clarithromycin (including intravenous clarithromycin) but chronic administrations are not permitted. Azithromycin may be used chronically and is recommended as the macrolide antibiotic of choice.
- Anti-epileptic treatments; and anti-tuberculous therapy.

These medications must all have been stopped at least 14 days prior to first dose of study treatment.

Sensitive narrow therapeutic index CYP3A4 substrates:
Nemiralisib is a time-dependent inhibitor of CYP3A4 and co-administration of CYP3A4 substrates with nemiralisib may result in increased systemic exposure to the CYP3A4 substrate. Regular or chronic treatment with medications that are considered sensitive narrow therapeutic index substrates of CYP3A4 are, therefore, not permitted:

- Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine and tacrolimus.

These medications must all have been stopped at least 14 days prior to first dose of study treatment.

- Intravenous and oral theophylline will be allowed according to the approved label/Prescribing Information, since a specific mechanistic model constructed for nemiralisib co-administered with theophylline, suggests a negligible effect of nemiralisib on theophylline exposure. Monitoring of patients receiving IV theophylline will be required in line with normal practice.
- Use of unstable dosing regimen with i.v. Ig / s.c. Ig in the last 6 months before screening. Stable maintenance immunoglobulin regimen, as per local practice, such as regular injections with a consistent dosing interval (e.g. monthly) is acceptable.
- Previous use of an mTOR antagonist (e.g. rapamycin, everolimus) or PI3K delta inhibitor (selective or non-selective PI3K inhibitors) within 6 weeks prior to first dosing.

RELEVANT HABITS
6. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >14 units. 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. 7. A positive pre-study drug screen. The detection of drugs (e.g. benzodiazepines, opioid analgesia) taken for a legitimate medical purpose would not necessarily be an exclusion to study participation and would be at the discretion of the principle investigator in discussion with the medical monitor.

CONTRAINDICATIONS
8. History of sensitivity to any of the study medications, or components thereof (including lactose) or a history of drug or other allergy (including a milk protein allergy) that, in the opinion of the investigator or Medical Monitor, contraindicates their participation. 9. History of previous intolerance of the induced sputum procedure. 10. BAL sub study only: History of bronchospasm in response to the bronchoscopy/BAL procedure.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
11. 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. 12. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 56 days. 13. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dose of study medication in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 14. A positive test for human immunodeficiency virus (HIV) antibody. 15. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dose of study medication.

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 Serious Adverse Events (Section 7.3.1.6).

Subjects who have failed screening may be re-screened once, at the discretion of the Principal Investigator in consultation with the GSK medical monitor.
In the event of a suspected exacerbation (as defined in Table 2), the subject will undergo an appropriate diagnostic and clinical work-up, with treatment including, but not limited to, antimicrobial treatment instituted as needed by the investigator or attending physician. Treatment should take local guidelines, especially on local antimicrobial resistance, into consideration. Any such subject will be allowed to be rescreened once following an exacerbation, after undergoing appropriate clinical review and when the Principal Investigator in consultation with the medical monitor consider the infection to have resolved.

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the study 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.

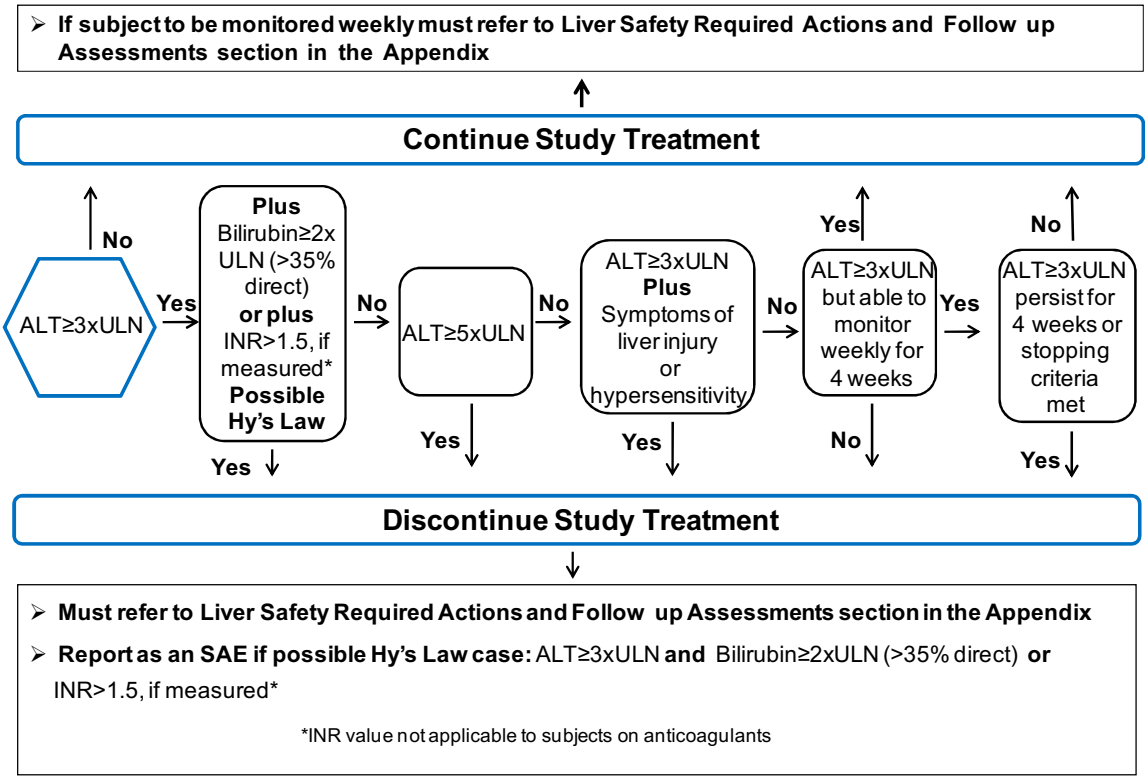
Subjects withdrawn from study treatment will also be withdrawn from the study. Subjects who are withdrawn should complete the assessments planned for the early withdrawal visit within 2 weeks of withdrawal (see Table 6). The subject will also receive a follow-up telephone call within 1−2 weeks after the last dose of study medication, if the early withdrawal visit was conducted during the first week following withdrawal. The reason for withdrawal will be recorded in the case report form (CRF)

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

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

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

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

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

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

5.4.3. Other Safety Stopping Criteria

A subject will be withdrawn from the study if they meet any of the following stopping criteria:

- Unacceptable adverse events related to study drug or study procedures.
- Clinically significant and relevant changes in laboratory parameters, spirometry or ECG recordings as judged by the Investigator, in consultation with the medical monitor if necessary
- Paradoxical bronchospasm.
- Pregnancy (female subjects).
- If during the study, a strong inhibitor of CYP3A4 is prescribed, the study drug should be stopped for the duration of the treatment with the strong inhibitor and not restarted for at least two-weeks after the strong inhibitor has been stopped. In the event that the co-prescribed drug cannot be stopped, the study drug should be permanently stopped and the patient withdrawn from the study.

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/contact.

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.

Table 3 Study Treatments

Product name:	**Nemiralisib ELLIPTA DPI (500 μg)**
Formulation description:	Nemiralisib blended with lactose and magnesium stearate in ELLIPTA DPI
Dosage form:	Dry powder for inhalation
Unit dose strength:	500 μg / blister
Route of Administration	Inhalation
Dosing instructions:	Inhale ONCE in the MORNING as directed

A patient instruction leaflet for the ELLIPTA DPI will be provided to all enrolled subjects.

6.2. Treatment Assignment

The study is an open-label design.

All subjects will be assigned nemiralisib 500 μg once daily.

A new randomisation will be produced to accommodate the inclusion of a third treatment arm into the study. This is to allow for the reporting of the data to be performed on a treatment level where appropriate.

6.3. Planned Dose Adjustments

Due to the small size of the study, no planned study level dose adjustments are allowed. Dose adjustment may be permitted at a subject level, however, as outlined in Section 6.4.

6.4. Subject Specific Dose Adjustment Criteria

In the event of adverse events, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator and/or medical monitor to dosing with nemiralisib, treatment will be halted and safety review of the subject will be undertaken.

6.5. Blinding

This will be an open-label study and investigators will have direct access to the subject's individual study treatment.

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).
- Damaged or faulty inhalers will be recorded and returned to GSK for further investigation. Full details of the process are contained in the study reference manual (SRM).
- Further guidance and information for final disposition of unused study treatment are provided in the 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 at the study 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 the counter reading after completing dose administration will be recorded. Compliance will be checked by the site staff at each planned visit.

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

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

6.9. Treatment of Study Treatment Overdose

For this study, any dose of nemiralisib > 1000 μg within a 24 hour time period ± 2 hours will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator, must:

1. Contact the Medical Monitor immediately
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until nemiralisib can no longer be detected systemically (at least 14 days for nemiralisib – though this will not be confirmed by direct measurement of plasma concentration)
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 safety and efficacy of nemiralisib has not yet been defined in APDS patients. Treatment after the end of the study will continue as per the standard of care for APDS at the site.

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

6.11. Lifestyle and/or Dietary Restrictions

Refrain from consumption of Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication until after the final dose.

6.11.1. Caffeine, Alcohol, and Tobacco

Subjects must refrain from alcohol for 24 hours prior to each blood collection for clinical laboratory tests.

Subjects must refrain from smoking for at least 2 hours prior to the respiratory tests, sputum induction and BAL (optional sub study) conducted at the study clinic.

6.11.2. Activity

Subjects must abstain from strenuous exercise for 24 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

6.12. Concomitant Medications and Non-Drug Therapies

6.12.1. Permitted Medications and Non-Drug Therapies

- **Decongestants:** Subjects may take decongestants, but must refrain for 24 hours prior to ECG measurements.
- **Intranasal corticosteroids:** Subjects may take intranasal corticosteroids to control symptoms of allergic disorders**.**
- **Topical corticosteroids:** Subjects may use topical corticosteroids for dermatological diseases.
- **Inhaled corticosteroids:** Subjects may take inhaled corticosteroids, if deemed appropriate, to manage underlying airway inflammation.
- **Immunotherapy for allergies:** Immunotherapy for the treatment of allergies is allowed, provided it was initiated 4 weeks prior to Screening and subjects remain in the maintenance phase for the duration of the study.
- **Antihistamines:** Short-acting and long-acting antihistamines, as well as antihistamine eye drops are allowed to control symptoms of allergic disorders
- **Influenza vaccination**
- **Pneumococcal vaccination**

All medications for other disorders may be continued throughout the study, provided that, in the opinion of the investigator (in consultation with the GSK Medical Monitor), their use will not affect the subject's lung function or safety assessments.

6.12.2. Prohibited Medications and Non-Drug Therapies

Concomitant use of inhibitors of CYP3A4 substrates is not permitted. Acute administration (up to 14-day dosing) of some of the 3A4 inhibitors is, however, permitted. See Section 6.2 Exclusion Criteria 5 for detail. Where clinically appropriate, an alternative drug in the same class (or unrelated class) that is not a strong CYP3A4 inhibitor can, after signing informed consent, be substituted for the original strong inhibitor of these enzymes (Table 4). If during the study, a strong inhibitor of CYP3A4 is prescribed, the study drug should be stopped for the duration of the treatment with the strong inhibitor and not restarted for at least two-weeks after the strong inhibitor has been stopped. In the event that the co-prescribed drug cannot be stopped, the study drug should be permanently stopped and the patient withdrawn from the study (see Section 5.4.3).

Use of unstable dosing regimen with i.v. Ig / s.c. Ig in the last 6 months before screening. Stable maintenance immunoglobulin regimen, as per local practice, such as regular injections with a consistent dosing interval (e.g., monthly) is acceptable.

Previous use of a PI3K delta inhibitor (selective or non-selective PI3K inhibitors) or mTOR antagonists within 6 weeks prior to first dosing

Table 4 Inhibitors of CYP3A4 substrates and alternatives

Class of Drug	CYP3A4 Inhibitors	Possible Alternative(s)
Macrolide antibiotics	clarithromycin	azithromycin
	troleandomycin	
	telithromycin	
	erythromycin	
Antifungal	itraconazole	amphotericin posaconazole
	ketoconazole	
	voriconazole	
	fluconazole	
Anti-retroviral (PI)	indinavir lopinavir/ritonavir nelfinavir	Tipranavir. Other classes e.g. NNRT
	ritonavir	
	saquinavir	

Class of Drug	CYP3A4 Inhibitors	Possible Alternative(s)
	atazanavir	
Anti-HCV (PI)	boceprevir	Other classes e.g. Ribavirin, Peginterferon alfa
	telaprevir	
Non-selective CaChB	mibrefradil	amlodipine
Non-peptide ADH inhibitor	conivaptan	
Anti-HT2 Antidepressant	nefazodone	Other classes
SSRI Anti-depressants	fluoxetine	fluvoxamine
	paroxetine	Other classes
Class IA Anti-arrythmic	quinidine	
Smoking cessation	buproprion	NRT
Immunosuppressant	cyclosporine	
	rapamycin	
	tacrolimus	
	everolimus	
Ergot alkaloid	ergotamine	
	dihydroergotamine	
Opioid	fentanyl	
	alfentanil	
Antipsychotic	pimozide	

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 Tables Section 7.1

The following points must be noted:

If assessments are scheduled for the same nominal time, THEN the assessments *should* occur in the following order:

1. physical examinations
2. vital signs
3. 12-lead ECG
4. lung function tests (spirometry)
5. blood draws
6. pregnancy test
7. sputum induction

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

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

The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.

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

No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

Table 5 Time and Events Table for Screening and Run-in Period

Procedure	Pre-Screening	Screening	Clinic visit #1	Notes
		(up to 42 days prior to dosing)	At least 7 days prior to dosing	
Informed consent	X			Pre-screening and screening may occur on the same visit, if appropriate
Concomitant medication review	X			
Review of exacerbation history	X			
Demography	X	X		
SAE review	X	X	X	
Inclusion and exclusion criteria		X		
Full physical exam, including height and weight		X		
Brief physical examination			X	
Medical history (includes substance usage and Family history of premature CV disease)		X		Substances: Drugs, Alcohol, tobacco
Past and current medical conditions (including ear, sinus and pulmonary infection history, cardiovascular medical history and therapy history)		X		
Vital signs (Blood pressure (BP), heart rate (HR), temperature and respiratory rate)		X	X	Triplicate measurements of BP and HR
12-lead ECG		X	X	Triplicate

Procedure	**Pre-Screening**	**Screening**	**Clinic visit #1**	**Notes**
		(up to 42 days prior to dosing)	**At least 7 days prior to dosing**	
Spirometry (incl. reversibility)		X		
Laboratory assessments (include hematology, biochemistry, Urinalysis)		X	X	
HIV, Hep B and Hep C screen		X		
Blood pregnancy test (only WCBP)		X		
PD blood sample: Lymphocyte assessments (subset counts, soluble proinflammatory mediators, phosphoprotein biomarkers, immunoglobulins.)			X	
PD blood sample: PIP_2/PIP_3 assessments			X	
PD blood sample: mRNA biomarkers			X	
PD blood sample: bacterial DNA fragment analysis			X	
Sputum induction			X	Should sputum induction fail or be insufficient, the subject will be allowed to return within 48 hours for a further attempt to obtain an adequate sample
BAL sub-study only: Bronchoscopy/BAL			*X*	*Performed on a different day to the sputum induction. For measurement of PD*
BAL sub-study only: Additional haematology assessments			*X*	*For clotting status (Activated partial thromboplastin time (aPTT), Prothrombin time (PT))*

Table 6 Time and Events Table for Treatment Period and Follow-up

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early withdrawal (within 2 wks)	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days	-4 / +2 days			±2 weeks	
In-Patient	X	X	X										
Out-Patient				X		X	X	X	X	X		X	
Telephone Contact/ Research nurse visit					X weekly						X		Except weeks where subjects have a clinic visit
SAFETY ASSESSMENTS													
Brief physical exam	X			X		X	X	X		X		X	Pre-dose
AE/SAE review	←==========→										X	X	
Concomitant medication review	←==========→										X	X	
Vital signs	X	X		X		X	X	X	X	X		X	Pre-dose. Single assessment
12-lead ECG	X	X		X		X	X	X		X		X	Pre-dose. Single assessment
Urine pregnancy test	X			X			X	X		X			only WCBP
Laboratory assessments (include haematology, biochemistry, Urinalysis)	X			X		X	X	X		X		X	Pre-dose
STUDY TREATMENT													
ELLIPTA inhaler training	X												Review of the Patient Information Leaflet with the subject (no device will be used). Additional training may be conducted at the discretion of the investigator
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

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early withdrawal (within 2 wks)	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days	-4 / +2 days			±2 weeks	
In-Patient	X	X	X										
Out-Patient				X		X	X	X	X	X		X	
Telephone Contact/ Research nurse visit					X weekly						X		Except weeks where subjects have a clinic visit
													be dosed at the clinic).
Assessment of study treatment compliance				X		X	X	X		X			
EFFICACY ASSESSMENTS													
Exit interview								X		X			Exit interview may be held at the study clinic or the subject's home, within 7 days of last dose.
OTHER ASSESSMENTS													
Review of APDS exacerbation and respiratory tract infection history				X		X	X	X		X	X	X	Including ear, sinus and pulmonary infections.
FEV1 Pre-Dose		X		X				X		X		X	For efficacy
FEV1 1hr Post-Dose		X	X	X									For safety
Blood sample for PK		X		X				X		X			Day 1: Pre-dose, 5 min, 3 h and 24 h post-dose. Pre-dose at all other visits.
PD blood sample: Lymphocyte assessments	X			X				X		X		X	Pre-dose. Subset counts, soluble proinflammatory mediators, phosphoprotein biomarkers, immunoglobulins.
PD blood sample: PIP_2/PIP_3 assessments	X			X				X		X		X	Pre-dose.

Procedure	**Treatment Period**										**Follow-up Period**		**Notes**
Clinic Visit	**2**			**3**		**4**	**5**	**6**		**Early withdrawal (within 2 wks)**	**1-2 wks and 4-6 wks**	**7**	
Day	**-1**	**1**	**2**	**14**	**2 to 84**	**28**	**56**	**83**	**84‡**			**3 mths**	
Visit window	**N/A**	**N/A**	**N/A**	**±2 days**	**±3 days**	**-4 / +2 days**	**-4 / +2 days**	**-4 / +2 days**	**-4 / +2 days**			**±2 weeks**	
In-Patient	X	X	X										
Out-Patient				X		X	X	X	X	X		X	
Telephone Contact/ Research nurse visit					X weekly						X		Except weeks where subjects have a clinic visit
PD blood sample: mRNA biomarkers	X			X				X		X		X	Pre-dose.
PD blood sample: bacterial DNA fragment analysis	X			X				X		X		X	Pre-dose.
Sputum induction	X			X				X				X	Pre-dose. Should sputum induction fail or be insufficient, the subject will be allowed to return within 48 hours for a further attempt to obtain an adequate sample
BAL sub-study only: Additional haematology assessments								X					*For clotting status (Activated partial thromboplastin time (aPTT), Prothrombin time (PT))*
BAL sub-study only: Bronchoscopy/BAL									X				For measurement of PK and PD
BAL sub-study only: Blood sample for urea PK									X				
BAL sub-study only: Blood sample for plasma PK									X				
Genetic Sample	X												Optional assessment – the subject must provide additional consent for the genetic sample. Genetic sample can be taken at any time after randomisation.

‡ Day 84 visit will only occur if a subject has agreed to take part in the BAL sub-study, dosing will continue until the D84 visit.

7.2. Screening and Critical Baseline Assessments

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

Ear, sinus and pulmonary infection history will be captured over the preceding 2 year period, including number, timing, pathogen (if known), and treatment.

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 patient'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.

7.3. 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 AEs/SAEs, vital signs, ECG, physical exams, spirometry and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. 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.

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

- 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.
- AEs will be collected from the start of Study Treatment until the three month follow-up visit (see Section 7.3.1.3), at the timepoints 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.
- 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 and Appendix 5

7.3.1.2. 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?"

7.3.1.3. 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.

7.3.1.4. 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.

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

An exacerbation of APDS is defined as a culture-documented or suspected bacterial, viral or fungal infection, either organ-specific (local) or systemic, which requires antimicrobial treatment or leads to a change in APDS management. This could include emergency room treatment or hospitalization.

APDS exacerbations, as defined above (Table 2), will be reported in the corresponding eCRF pages. APDS exacerbations are associated with the disease to be studied, so will not be recorded as AEs unless they meet the definition of SAE, as defined in Appendix 4.

APDS exacerbations that meet the definition of SAE will be recorded on the appropriate SAE form, and will be reported to GSK, as stated in Appendix 4

7.3.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs 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.

7.3.2. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of dosing and until the 3 month follow-up visit.

Details of pregnancies for female partners of male participants will not be routinely collected; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism.

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.

7.3.3. 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 must pay special attention to clinical signs related to previous serious illnesses

7.3.4. Vital Signs

Vital signs will be measured (triplicate at screening) in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.

7.3.5. Electrocardiogram (ECG)

Single 12-lead ECGs (triplicate at screening) will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

7.3.6. Spirometry

7.3.6.1. FEV_1 (1 hr Post-dose)

FEV1 will be measured using a spirometer at the time indicated in the time and events table [Section 7.1]. All sites will use their existing spirometry equipment.

Subjects should not use their rescue medication for at least 4 hours before each FEV_1 assessment, unless essential for clinical need.

For each observation, at least 3 valid (with no more than 8) efforts will be obtained in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [Miller, 2005]. Record 3 FEV1 measurements in the CRF

A full description of the timing and conduct of spirometry procedures will be provided in the SRM.

7.3.6.2. (Screening Only) Bronchodilator Responsiveness Testing (reversibility)

At screening, reversibility in FEV_1 will be assessed. Reversibility evaluations must follow the recommendations of the ATS/ERS task force [Miller,2005].

FEV_1 will be measured pre-salbutamol and within 10 to 40 minutes following 400 mcg salbutamol MDI – 4 inhalations of 100 mcg (a spacer device may be used if required).

Percent reversibility will be calculated as follows:

$$\left(\frac{\text{Post} - \text{bronchodilator FEV1} - \text{Pre} - \text{bronchodilator FEV1}}{\text{Pre} - \text{bronchodilator FEV1}}\right) \times 100$$

7.3.7. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 7, 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.

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

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 7.

Table 7 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Haematology	Platelet Count	*Red blood cells (RBC) Indices*:	*White blood cells (WBC) count with Differential:*
	RBC Count	Mean corpuscular volume (MCV)	Neutrophils
	Hemoglobin	Mean corpuscular hemoglobin (MCH)	Lymphocytes
	Hematocrit		Monocytes
	Activated partial thromboplastin time (aPTT)[3]		Eosinophils
	Prothrombin time (PT)[3]		Basophils

Laboratory Assessments	**Parameters**			
Clinical Chemistry [1]	Blood urea nitrogen (BUN)/Urea	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose (non fasted)	Calcium	Alkaline phosphatise	Albumin
	CRP			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum or urine hCG Pregnancy test (as needed for women of child bearing potential) [2]			

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.
3. *BAL sub-study only*: Day 1 Clinic Visit #1, and Day 83 -4/+2 days.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology must be identified and the sponsor notified.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

A 2 mL blood sample for PK analysis of nemiralisib will be collected at the time points indicated in Section 7.1 Time and Events. The actual date and time of each blood sample collection will be recorded. In addition, the date and time of dosing on the days prior to Day 14 and 28 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 SRM.

7.4.2. Urea Blood Sample

Collect a 2ml blood sample into Lithium Heparin tubes ***either*** at the same time as the Day 84 trough PK sample if BAL occurs on or *before* 12 noon ***or*** as soon as practically possible after the BAL samples if BAL occurs *after* 12 noon.

Processing, storage and shipping procedures are provided in the SRM.Bronchoalveolar Lavage (BAL) Sample Collection

BAL samples for pharmacokinetic analysis of nemiralisib will be collected during the bronchoscopy at the time point listed in Section 7.1. Details of BAL sample collection can be found in Section 7.6. Processing, storage and shipping procedures are provided in the SRM.

7.4.3. Sample Analysis

Plasma analysis for nemiralisib will be performed under the control of PTS- Drug Metabolism and Pharmacokinetics (DMPK)/Scinovo, GlaxoSmithKline. Lung epithelial lining fluid (ELF) and BAL cell pellet analysis for nemiralisib will be performed under the management of PTS-DMPK, GlaxoSmithKline. Concentrations of nemiralisib will be determined using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Plasma and lavage analysis for urea quantification will be performed under the management of Clinical Pathology, Safety Assessment, GlaxoSmithKline. Concentrations of urea will be determined in plasma and lavage samples using the currently approved analytical methodology. Raw data will be stored in the good laboratory practice (GLP) Archives, GlaxoSmithKline.

7.5. Biomarker(s)/Pharmacodynamic Markers

7.5.1. Pharmacodynamic Biomarkers in Blood

The following blood samples will be collected for PD analysis of nemiralisib at the time points indicated in Section 7.1 Time and Events:

- 5 mL for analysis of cellular PIP3 peak area
- 20 mL for lymphocyte assessments (subset counts, soluble proinflammatory mediators, phosphoprotein biomarkers, immunoglobulins)
- 2.5 mL for analysis of messenger ribonucleic acid (mRNA) biomarkers
- 5 mL for bacterial DNA fragment analysis

The actual date and time of each blood sample collection will be recorded. The timing of PD samples may be altered and/or PD samples may be obtained at additional time points to ensure thorough PD monitoring.

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

7.5.2. Pharmacodynamic Biomarkers in Induced Sputum

Hypertonic saline (starting at a concentration of 0.9%) induced sputum samples will be collected. The sputum induction process is detailed in the SRM.

Should sputum induction fail or be insufficient, the subject may return within 48 hours for a further attempt to obtain an adequate sample.

To maximise the ability to measure multiple PD markers, the sputum samples will be assessed for *either* PIP/PIP3 ratio *or* cytokines and mRNA transcriptome (detailed in Table 8) at different time points before and after administration of nemiralisib. Upon the review of data from the first two subjects this approach could be altered to focus on only PIP/PIP3 ratio or the range of cytokines and mRNA transcriptome at all time points. Additional parameters may be analysed if sufficient induced sputum sample is available once samples for the other assessments have been collected.

Further information on collection, processing, storage and shipping procedures are provided in the Study Reference Manual.

Table 8 Proposed Biomarkers for Analysis in Sputum Samples

	PIP2/ PIP3	Lymphocyte subsets	Phospho-proteins	Inflammatory mediators	mRNA
Clinic visit #1	X				
Day -1		X	X	X	X
Day 14	X				
Day 83		X	X	X	X
6m Follow-up (3m post-dose)*		X	X	X	X

* Assessment of PIP2/PIP3 ratio may replace other measurements at the 6m follow-up time-point, based on the assessment of the data at prior time-points.

7.6. Bronchoscopy/BAL (*BAL sub-study only)*

- Bronchial alveolar lavage (BAL) will be collected at bronchoscopy at the time indicated in the time and events table [Section 7.1].
- The bronchoscopy must be conducted by an experienced bronchoscopist in accordance with the guidelines published by the British Thoracic Society [Du Rand, 2013].
- The right middle lobe (RML) will be preferentially selected for lavage unless historical thoracic CT/chest X-ray (when available) indicate significant underlying structural lung disease/abnormality. In cases where the RML is not considered appropriate, an alternative lobe will be selected after review and discussion between the bronchoscopist, PI and medical monitor. In instances where historical thoracic CT/chest X-rays are not available, the RML will be selected.

- Providing sufficient sample volume is available, samples will be processed and analysed for the biomarkers as detailed in Table 9. In the event of insufficient sample being available, priority will be given to the measurement of inflammatory mediators and lymphocyte subsets.
- Further information on collection, processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

Table 9 Proposed Analysis of BAL

Sample fraction	Pharmacokinetics		Pharmacodynamic Markers			
	PK	Urea	Inflammatory mediators	Antibody levels	Lymphocyte subsets	Proteomics
Epithelial Lining Fluid	X	X	X	X		**X**
Cell pellet	X				X	

7.7. Efficacy

7.7.1. Number and rate of lower/upper respiratory tract infection

The number and rate of ear, sinus and/or pulmonary infections requiring antimicrobial therapy will be monitored and recorded.

7.7.2. FEV1 (Pre-dose)

FEV1 will be measured using a spirometer at the times indicated in the time and events table [Section 7.1]. All sites will use their existing spirometry equipment.

For each observation, at least 3 valid (with no more than 8) efforts will be obtained, in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [Miller, 2005].

Pre-dose FEV1 measured on Day 14, Day 83 or upon early withdrawal should be within ±1 hour of the time FEV1 was measured on Day 1.

Subjects should not use their rescue medication for at least 4 hours before each FEV1 assessment, unless essential for clinical need. If a subject uses their rescue medication within 4 hours of the FEV1 assessment, the subject may be asked to return within 48 h for another attempt.

Further details are provided in the SRM

7.7.3. Patient Exit Interview

An exit interview will be administered to all study participants (within 7 days of final visit or early withdrawal). The questions included in the interview will be designed to more fully understand the patient's experience with APDS, the respiratory aspects of the disease that are most important to them, the perceived efficacy of the study medication and the study itself. Subjects will be asked to consent to the exit interview within the context of study consent.

A specialist contract research organisation will be commissioned to conduct this part of the study. The organisation will develop a protocol for conducting the exit interviews, a semi-structured interview guide and data collection sheet and the qualitative analysis plan. The contract research organisation (CRO) will conduct the interviews using an experienced qualitative interviewer, analyse the data from the interviews and provide a final report and supporting documentation. Interviews will be audio recorded for the purposes of accurate analysis.

This assessment will be completed by all study participants and may be held at the study clinic or the subject's home. The exit interview will be conducted, transcribed and analysed in English as outlined in the Interview Discussion Guide.

7.8. 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.
- Adverse Events and concomitant medications taken.

7.9. Genetics

Information regarding genetic research is included in Appendix 3.

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 Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.

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

9.1. Sample Size Considerations

The sample size for this study is based on the feasibility of recruitment of this population.

9.2. Data Analysis Considerations

9.2.1. Analysis Populations

Population	Definition / Criteria
Screened	• All subjects who were screened
All subject	• All subjects who receive at least one dose of the study treatment.

9.3. Key Elements of Analysis Plan

9.3.1. Interim Analyses

Formal interim analyses will not be performed. However, safety and pharmacodynamic data will be reviewed on an ongoing basis for internal decision making purposes, to ensure subject safety and in order to maximise the ability to measure multiple PD markers, based on sample availability (as discussed in Section 7.5.2). Further details are provided in the RAP.

9.3.2. Primary Analyses

Safety data will be graphically presented, summarised and listed by, or under the direct auspices of, Clinical Statistics, GlaxoSmithKline.

Statistical analyses, when applicable, of safety data will be performed by, or under the direct auspices of, Clinical Statistics, GlaxoSmithKline.

The three formulations of nemiralisib may be presented by treatment arm or pooled where appropriate. Full details of all statistical analyses will be pre- specified in the RAP prior to unfreezing of the database.

9.3.2.1. Exploratory Biomarker Analyses

The results of exploratory biomarker investigations (e.g. bacterial DNA fragment analysis) may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

9.3.3. Patient Exit Interview

The qualitative data collected in the patient exit interviews will be analyzed separately by outsourcing to a specialist consultant.

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
- Obtaining signed informed consent
- 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 (SOP).

- 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.

- 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.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

µg	Microgram
µL	Microliter
AE	Adverse Event
AICD	activation induced cell death
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of Variance
APDS	Activated PI3K Delta Syndrome
AST	Aspartate aminotransferase (SGOT)
ATS	American Thoracic Society
BAL	Bronchial alveolar lavage
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary diseases
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacokinetics Modelling & Simulation
CRF	Case Report Form
CV	Cardiovascular
CYP	Cytochrome P
DBP	Diastolic blood pressure
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
ELF	Epithelial Lining Fluid
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IL	Interleukin
IP	Investigational Product
IRB	Institutional Review Board
IU	International Unit
I-V	Intravenous
Kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MgSt	Magnesium Stearate
mL	Milliliter
MMP9	Matrix metallopeptidase 9
mRNA	Messenger ribonucleic acid
MSDS	Material Safety Data Sheet
msec	Milliseconds
OD	Once daily
PASLI	p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency
PD	Pharmacodynamic
PI3K	Phosphoinositide 3-Kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PK	Pharmacokinetic
PoC	Proof-of-Concept
PSRI	Periodic Safety Reports for Investigators
QC	Quality control
QD	Once daily
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
SRM	Study Reference Manual
TNF	Tumor necrosis factor
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UV	ultraviolet

VOC	Volatile Organic Chemical
WBC	White blood cells

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)
INR[2]	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/** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (Appendix 4) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the 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

for any protocol specified follow up assessments **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	form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<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.

12.3. Appendix 3 - Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

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;
- APDS 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). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

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

Events NOT meeting definition of an AE include:
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.

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

Cardiovascular Events (CV) Definition:
• 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. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. • The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

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

Assessment of Intensity
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 - Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. 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.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- 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, 2011].
- Male condom plus partner use of one of the contraceptive options below:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
    - Injectable progestogen [Hatcher, 2011]
    - Contraceptive vaginal ring [Hatcher, 2011]
    - Percutaneous contraceptive patches [Hatcher, 2011]

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH M3 (R2), 2009].

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. 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 24 hours 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.

Male participants with partners who become pregnant

- Investigator will not routinely attempt to collect pregnancy information on any male participant's female partner(s) who becomes pregnant while the male participant is participating in this study; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism.
- If pregnancy information for a male participant's female partner(s) is voluntarily reported, after obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.6. Appendix 6 - Protocol Amendment Changes

AMENDMENT 1

Where the Amendment Applies

This amendment applies to all investigator sites participating in this study.

Summary of Amendment Changes with Rationale

The protocol has been amended as follows:

1. Minor change to the wording of the exploratory efficacy endpoint has been made.
2. Reference to randomisation of subjects removed for clarity and accuracy.
3. Mitigation strategy of the APDS exacerbation risk has been updated to ensure consistency with the weeks the clinic visits occur on, as described in the protocol
4. Removal of instruction on the need for precautionary measures to protect against potential photosensitive effects of GSK2269557 (following new non-clinical data supporting the discharge of this risk to humans)
5. Maximum weekly alcohol consumption for males reduced from 21 to 14 units. Updated to reflect current UK guideline following the recent change in advice.
6. Additional exclusion criteria added to exclude subjects who provide a positive sample in a pre-study drug screen.
7. Immunoglobulins added to the list of PD lymphocyte assessments to provide further characteristics pertaining to lung infection in APDS patients.
8. Time and Events Table for Screening and Run-in Period updated as follows:
    - Immunoglobulins added to the list of PD lymphocyte assessments
    - Timing of PD sample collection for bacterial DNA fragment analysis added and to ensure consistency with body text.
    - Laboratory tests for clotting status added to clinical visit #1 for subjects consenting to the BAL sub-study.
9. Time and Events Table for Treatment Period and Follow-up updated as follows:
    - Timing of reviews of APDS exacerbation and respiratory tract infection history added to make consistent with body text.
    - Day 2 PK blood sample (which refers to Day 1 24 hr timepoint) removed from table for clarity
    - Immunoglobulins added to the list of PD lymphocyte assessments
    - Timing of PD sample collection for bacterial DNA fragment analysis added to ensure consistency with body text.
    - Laboratory tests for clotting status added to Day 83 (-4/+2) for subjects consenting to the BAL sub-study.

10. Removal of 'severity of infection' as a measurement taken during the screening and critical baseline assessments
11. Clarification of the period during which details of pregnancies in female subjects will be collected after the start of dosing
12. Addition of two haematology laboratory tests for clotting status to be performed at clinical visit #1 and Day 83 (-4/+2) for subjects consenting to the BAL sub-study.
13. Clinical Chemistry section amended to clarify that blood glucose test is a non-fasting measurement.
14. Additional text added to clarify which lung lobe will be targeted during the BAL procedure.
15. Proposed analyses of BAL updated to indicate that proteomic analysis will be performed on the Epithelial Lining Fluid not the cell pellet.
16. Additional text added to analysis section to clarify the timing of reporting of exploratory biomarker data to ensure publication of data pertaining to core primary and secondary measures is not delayed.

List of Specific Changes (Bold text depicts new text while strike through text depicts deleted text)

Change 1:

The wording of the exploratory efficacy endpoint has been modified:

Page 11. Section 1. PROTOCOL SYNOPSIS FOR STUDY

The ~~frequency and~~ number **and rate** of pulmonary and/or ear and sinus infections requiring anti-microbial treatment compared to subject's historical baseline

Page 13. Overall design. Follow up period.

Subjects will receive telephone calls at 1-2 weeks and 4-6 weeks after their last dose. These will be used to ensure there are no safety concerns and to monitor the ~~frequency and~~ number **and rate** of lower/upper respiratory tract infections requiring antimicrobial therapy.

Page 16. Section 3. OBJECTIVE(S) AND ENDPOINT(S). Exploratory Efficacy Endpoint:

The ~~frequency and~~ number **and rate** of pulmonary and/or ear and sinus infections requiring anti-microbial treatment compared to subject's historical baseline

Page 18. Section 4.2.Treatment Arms and Duration. Follow up period:

Subjects will receive telephone calls at 1-2 weeks and 4-6 weeks after their last dose. These will be used to ensure there are no safety concerns and to monitor the frequency ~~frequency and~~ number **and rate** of lower/upper respiratory tract infections requiring antimicrobial therapy

Page 54. Section 7.7.1. Frequency of lower/upper respiratory tract infection

7.7.1. ~~Frequency~~ Number and rate of lower/upper respiratory tract infection

The ~~rate and~~ number **and rate** of ear, sinus and/or pulmonary infections requiring antimicrobial therapy will be monitored and recorded.

Rationale 1

Updated for clarity as frequency and number allude to the same measurement. Rate of infection more accurately describes the intended parameter.

CHANGE 2:

Reference to randomisation removed for clarity and accuracy.

Page 11. Section 1. Overall Design

This is a multi-centre, ~~non-randomised,~~ open-label, uncontrolled, single group, study in patients with APDS.

Page 17. Section 4.2. Overall Design

This is be a multi-centre, ~~non-randomised,~~ open-label, uncontrolled single group study in patients with APDS.

Page 34. Section 6.2. Treatment Assignment

The study is a ~~non-randomised~~, open-label design.

Page 56. Section 9.2.1. Analysis Populations

Population	Definition / Criteria
Screened	• All subjects who were screened
All subject	• All ~~randomised~~ subjects who receive at least one dose of the study treatment.

Rationale 2

Subjects are randomized to study treatment for statistical purposes so the use of 'non-randomised' is inaccurate. Reference to subjects being 'randomised' has also been removed in order to remove any potential for confusion with the open-label design.

CHANGE 3:

Text for the mitigation strategy of the APDS exacerbation risk modified:

Page 20. Section 4.6.1. Risk Assessment. Table 1:

Subjects will visit the study clinic frequently (week 2, ~~6,~~ **4, 8** and 12)

Rationale 3

Updated to be consistent with the weeks the clinic visits occur on, as described in the protocol.

CHANGE 4:

Removal of text in Risk Assessment that described precautionary measures to be taken by participating patients in order to protect against potential photosensitive effects.

Page 22. Section 4.6.1. Risk Assessment. Table 1, Row 3.

~~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).~~

Page 37. Section 6.11. Lifestyle and/or Dietary Restrictions. Paragraph 1

Removal of text that described precautionary measures to be taken by participating patients in order to protect against potential photosensitive effects:

~~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 of study medication. Subjects are to be advised that they should wear protective clothing (e.g. sun hat, long sleeves) and use a broad spectrum UVA/UVB sunscreen (SPF ≥ 30) when outdoors.~~

Rationale 4

The availability of data from a completed *in-vivo* study supporting the removal of phototoxicity precautions.

CHANGE 5:

Maximum weekly alcohol consumption for males reduced from 21 to 14 units.

Page 27. Section 5.3. Exclusion Criteria. Relevant Habits - Number 8.

History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of ~~>21 units for males or >14 units for females~~ >**14 units.** 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.

Rationale 5

Updated to reflect current UK guideline following the recent change in advice.

CHANGE 6:

Additional exclusion criteria added to exclude subjects who provide a positive sample in a pre-study drug screen.

Page 29. Section 5.3. Exclusion Criteria. Relevant Habits - Number 9

ADDED TEXT

A positive pre-study drug screen. The detection of drugs (e.g. benzodiazepines, opioid analgesia) taken for a legitimate medical purpose would not necessarily be an exclusion to study participation and would be at the discretion of the principle investigator in discussion with the medical monitor.

Page 50. Section 7.3.7. Clinical Safety Laboratory Assessments.

Table 6. Other screening tests

ADDED BULLET

- **Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)**

Rationale 6

To remove subjects who are taking substances which may have an adverse interaction with the study drug or adversely impair study participation and compliance with study procedures.

CHANGE 7:

Immunoglobulins added to the list of PD lymphocyte assessments**.**

Page 52. Section 7.5.1. Pharmacodynamic Biomarkers in Blood

15. 20 mL for lymphocyte assessments (subset counts, soluble proinflammatory mediators, phosphoprotein biomarkers, **immunoglobulins**)

Rationale 7

To provide further characteristics pertaining to lung infection in APDS patients.

CHANGE 8:

Page 41. Section 7.1. Time and events table for Screening and Run-in Period updated as follows:

Table 4. Row 17

Immunoglobulins added to the list of PD lymphocyte assessments**.**

PD blood sample: Lymphocyte assessments (subset counts, soluble proinflammatory mediators, phosphoprotein biomarkers, **immunoglobulins**)

Table 4. Row 20.

New row added to T&E tables to clarify the timing of PD sample collection for bacterial DNA fragment analysis and to make consistent with body text.

Procedure	*Pre-Screening*	*Screening*	*Clinic visit #1*	*Notes*
PD blood sample: bacterial DNA fragment analysis			**X**	

Table 4. Row 23.

Row added to reflect the additional haematology tests which will be performed at clinic visit #1:

Procedure	*Pre-Screening*	*Screening*	*Clinic visit #1*	*Notes*
BAL sub-study only: Additional haematology assessments			***X***	***For clotting status (Activated partial thromboplastin time (aPTT), Prothrombin time (PT))***

Rationale 8

To provide clearer and consistent instruction on when procedures should be performed during screening and clinic visit #1.

CHANGE 9:

Page 43, Section 7.1. Time and Events for Treatment Period and Follow-up updated as follows:

Table 5. Row 15.

New row added to T&E tables to clarify the timing of reviews of APDS exacerbation and respiratory tract infection history and to make consistent with body text.

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early withdrawal	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days					
Review of APDS exacerbation and respiratory tract infection history				**X**		**X**	**X**	**X**		**X**	**X**	**X**	**Including ear, sinus and pulmonary infections.**

Table 5. Row 17.

Day 2 PK blood sample (which refers to Day 1 24 hr timepoint) removed from table for clarity and to avoid a duplicate blood sample being taken in addition to the Day 1, 24 hr sample.

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early withdrawal	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days					
Blood sample for PK		X	~~X~~	X				X		X			Day 1: Pre-dose, 5 min, 3 h and 24 h post-dose. Pre-dose at all other visits.

Table 5. Row 19.

Pre-dose. Subset counts, soluble proinflammatory mediators, phosphoprotein biomarkers, **immunoglobulins.**

Table 5. Row 21.

New row added to T&E tables to clarify the timing of PD sample collection for bacterial DNA fragment analysis and to make consistent with body text.

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early withdrawal	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days					
PD blood sample: bacterial DNA fragment analysis	**X**			**X**				**X**		**X**		**X**	**Pre-dose.**

Table 5. Row 24.

Row added to reflect the additional haematology tests which will be performed at Day 83 (-4 /+2):

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early withdrawal	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days					
BAL sub-study only: Additional haematology assessments								**X**					***For clotting status (Activated partial thromboplastin time***

Procedure	Treatment Period									Early withdrawal	Follow-up Period		Notes
Clinic Visit	2			3		4	5	6			1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days					
													(aPTT), Prothrombin time (PT))

Rationale 9

To provide clearer and consistent instruction on when procedures should be performed during the treatment and follow-up periods

CHANGE 10:

Removal of 'severity' of historical infections as a parameter captured during screening.

Page 46. Section 7.2. Screening and Critical Baseline Assessments

Ear, sinus and pulmonary infection history will be captured over the preceding 2 year period, including number, timing, pathogen (if known), ~~severity (if known)~~ and treatment.

Rationale 10

Information unlikely to be available or will be unreliable due to degree of subjectivity in the assessment.

CHANGE 11:

Clarification of the period during which details of pregnancies in female subjects will be collected after the start of dosing

Page 48. Section 7.3.2. Pregnancy

Details of all pregnancies in female subjects and if indicated female partners of male subjects will be collected after the start of dosing and until the **3 month** follow-up **visit** ~~call.~~

Rationale 11

To ensure that instances of pregnancies are collected for sufficiently long enough to ensure that the chance of a fetus being exposed to the study drug is minimized.

CHANGE 12:

Haematology section of Table 6, updated to allow two additional tests (aPTT and PT) to assess clotting status in subjects consenting to participate in the BAL sub-study:

Page 50. Section 7.3.7. Clinical Safety Laboratory Assessments.

Haematology. Table 6.

Haematology	Platelet Count	*Red blood cells (RBC) Indices*:	*White blood cells (WBC) count with Differential:*
	RBC Count	Mean corpuscular volume (MCV)	Neutrophils
	Hemoglobin	Mean corpuscular hemoglobin (MCH)	Lymphocytes
	Hematocrit		Monocytes
	Activated partial thromboplastin time (aPTT)[3]		Eosinophils
	Prothrombin time (PT)[3]		Basophils

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.
3. ***BAL sub-study only*: Day 1 Clinic Visit #1, and Day 83 -4/+2 days.**

Rationale 12

To ensure patients consenting to participate in the BAL study and undergoing bronchoscopy do not have evidence of an underlying coagulopathy that would preclude bronchoscopy. This is consistent with clinical best practice. Addition of tests for activated partial thromboplastin time (aPTT) and prothrombin time (PT) for patients who consent to BAL procedure required to ensure clotting factors are normal ahead of BAL procedure.

CHANGE 13:

Clinical Chemistry section of Table 6, amended to indicate that blood glucose test is a non-fasting measurement

Page 50. Section 7.3.7. Clinical Safety Laboratory Assessments. Clinical Chemistry. Table 6.

Clinical Chemistry [1]	Blood urea nitrogen (BUN)/Urea	Potassium	AST (SGOT)	Total and direct bilirubin	
	Creatinine	Sodium	ALT (SGPT)	Total Protein	
	Glucose **(non-fasted)**	Calcium	Alkaline phosphatise	Albumin	
	CRP				

Rationale 13

To clarify that subjects do not need to fast prior to glucose test.

CHANGE 14:

Additional text added to clarify which lung lobe will be targeted during the BAL procedure.

Page 53. Section 7.6. Bronchoscopy/BAL (BAL sub-study only).

ADDED BULLET #3

- **The right middle lobe (RML) will be preferentially selected for lavage unless historical thoracic CT/chest X-ray (when available) indicate significant underlying structural lung disease/abnormality. In cases where the RML is not considered appropriate, an alternative lobe will be selected after review and discussion between the bronchoscopist, PI and medical monitor. In instances where historical thoracic CT/chest X-rays are not available, the RML will be selected.**

Rationale 14

To provide clearer instruction with regard which lung lobe to target for the BAL to ensure the sample is obtained from the most relevant area of the lung.

CHANGE 15:

Page 54. Section 7.6. Bronchoscopy/BAL (BAL sub-study only).

Table 8. Proposed Analysis of BAL

Proposed analyses of BAL updated to indicate that proteomic analysis will be performed on the Epithelial Lining Fluid *not* the cell pellet, as currently stated.

Rationale 15

Correction of a previous error.

CHANGE 16:

Additional text added to analysis section to clarify the timing of reporting of exploratory biomarker data.

Page 56. Section 9.3.2.1. Exploratory Biomarker Analyses

The results of exploratory biomarker investigations (e.g. VOC in breath and bacterial DNA fragment analysis) may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

Rationale 16

To ensure publication of data pertaining to core primary and secondary measures is not delayed for exploratory endpoint data.

AMENDMENT 2

Where the Amendment Applies

This amendment applies to all investigator sites participating in this study.

List of Specific Changes and Rationale (Bold text depicts new text while strike through text depicts deleted text)

Change 1:

Replace the administration of GSK2269557 via the DISKUS device (1000 μg) by a comparable dose administered via the ELLIPTA device (700 μg)

Throughout the protocol: change "1000 μg" to "700 μg" and "DISKUS" to "ELLIPTA"

Page 21/22, Section 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 up to 84 days (-4/+2 days) **and is expected to be equivalent to a dose of 1000 μg administered via DISKUS in terms of the dose deposited and retained within the lungs based on PK parameters (AUC and Ctrough).** This dose has been selected based on previous safety and tolerability data in humans (healthy subjects, **healthy** smokers and COPD patients including exacerbating patients **following GSK2269557 administration via a DISKUS DPI, and healthy subjects via ELLIPTA DPI),** as well as **pharmacokinetics and** demonstration of target (PI3Kδ) inhibition by observed changes in biomarkers. This will be the first time GSK2269557 is dosed to patients who have been identified as having APDS, and it is assumed that these patients will have a similar lung deposition, distribution and plasma exposure to healthy volunteers and COPD patients (who had similar exposure). Twice the proposed dose (2000 μg **in DISKUS**) using the same formulation has previously been given once daily to healthy male smokers for 14 days (study PII116617) **and to** ~~. A total daily dose up to 2000 μg of GSK2269557 is currently being studied in~~ stable COPD patients ~~via a dry powder inhaler for 14 days~~ (study PII115119**). A total daily dose of 1000 μg is currently being studied in** exacerbating COPD patients for 3 months (study PII116678 **and study 201928**) and patients with persistent, uncontrolled asthma for 28 days **(study 201543).**

The target site of action for inhaled PI3Kδ inhibition is the intracellular compartment of immune cells resident in lung tissue and lumen. GSK2269557 has a high potency and selectivity at the PI3Kδ enzyme (Ki value **0.1** ng/mL). The pathophysiology of APDS is not fully understood, but is believed to involve a significant neutrophil component as well as T/B-cell and leukocyte driven effects. The predicted steady-state intracellular concentration of GSK2269557 at trough (24h) in the lungs of APDS patients is about 183 ng/mL (3.8 ng/mL free drug), implying PI3Kδ inhibition in excess of 80% throughout the inter-dosing interval in all cell types of interest. Systemic and tissue concentrations are

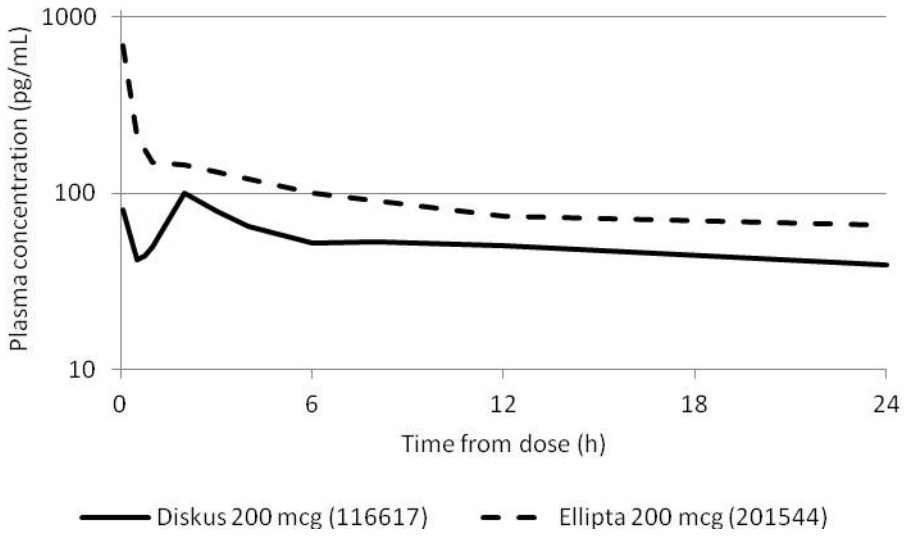
predicted to be extremely low (Cmax of 1.8 ng/mL, 0.04 ng/mL free drug), implying very little PI3Kδ inhibition **(<30%)** outside of the lung.

During the development of GSK2269557 as a dry powder for inhalation a switch has been made both in terms of device (to ELLIPTA) as well as formulation (addition of magnesium stearate as a formulation stabiliser). PK data has been used to calculate an equivalent 1000 μg dose from DISKUS in the ELLIPTA delivered drug product. Plasma PK data obtained from study 201544 with ELLIPTA DPI (part B, 200 μg OD for 14 days) (study completed but report not yet available) showed about 35% increase in systemic exposure compared to the steady state exposure of GSK2269557 following DISKUS DPI in study PII116617, Under the assumption that the ratio of intracellular concentration of GSK2269557 at trough in the lungs of APDS patients and plasma concentration stays the same, it is expected that 700 μg ELLIPTA DPI will produce similar PI3Kδ inhibitions in the lungs as that with 1000 μg DISKUS DPI.

Figure 2 shows the single dose day 1 median concentration time data derived from study 201544 when healthy volunteers were dosed with 200 μg via the ELLIPTAdevice together with the data for DISKUS derived from study PII116617 (extrapolated down from the 500 μg data). The 35% difference can clearly be seen in particular in the latter time points. The 35% increase in exposure (AUC and C_{trough}) is reflective of an observed increase in respirable mass as measured by *in vitro* drug product performance (Aerodynamic Particle Size Distribution). In addition to the overall increase in respirable mass there is a change in the distribution within the respirable mass fraction, with the magnesium stearate formulation of the ELLIPTA DPI producing a higher level of very fine particles. The approximate 350% increase seen in the C_{max} is believed to be reflective of this difference in distribution. The very fine particles are predicted to be deposited more to the alveolar region and hence absorbed more rapidly therefore contributing to the initial C_{max}. It is assumed that the increase in C_{trough} is reflective of the additional drug being deposited in the peripheral compartment (in this case the effect compartment of the resident cells of the lung) and it's therefore this measure which has defined the appropriate comparator to compare the two devices to match effect compartment exposure response.

The increased C_{max} in the ELLIPTA device would result in a median Day 1 concentration of approx 1.4 ng/mL achieving approximately 3.1 ng/mL at steady-state (> Day 6) which would still result in a low level of systemic pharmacology at peak of approximately 23 or 39% inhibition respectively whilst maintaining pharmacology (≥ 80%) in the lungs. However these peak levels are likely to drop off rapidly in plasma as can be seen in Figure 2.

Figure 2 Median Plasma Concentrations Post Single Inhaled Dose in Healthy Volunteers Following Dosing via Either DISKUS or ELLIPTA



Page 37, Section 6.1. Investigational Product and Other Study Treatment:

Product name:	GSK2269557 ~~DISKUS~~ **ELLIPTA** DPI (500 μg)	**GSK2269557 ELLIPTA DPI (100 μg)**
Formulation description:	**GSK2269557 blended with lactose and magnesium stearate in ELLIPTA DPI**~~Lactose blend containing GSK2269557 in DISKUS DPI~~	**GSK2269557 blended with lactose and magnesium stearate in ELLIPTA DPI**
Dosage form:	Dry powder for inhalation	**Dry powder for inhalation**
Unit dose strength:	500 μg / blister	**100 μg / blister**
Route of Administration	Inhalation	**Inhalation**
Dosing instructions:	**Inhale as directed**	**Inhale as directed**
~~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 study clinic. On those days, they will be dosed at the clinic). The subject should hold their breath for 10 seconds before exhaling. Inhalations should be taken approximately 30 seconds apart~~	

A patient instruction leaflet for the ELLIPTA DPI will be provided to all enrolled subjects. ~~Demonstration inhalers will be provided to each site in order for the investigator to demonstrate correct use of the DISKUS DPI to subjects. The demonstration inhalers will be marked clearly with bright yellow labels.~~

Page 37, Section 6.2. Treatment Assignment

A new randomisation will be produced to accommodate the inclusion of a second treatment arm into the study. This is to allow for the reporting of the data to be performed on a treatment level where appropriate.

Page 37, Section 6.9., Treatment of Study Treatment Overdose

For this study, any dose of GSK2269557 > ~~2000~~ **1400** µg within a 24 hour time period ± 2 hours will be considered an overdose.

Page 60, Section 9.3.2. Primary Analyses

The two formulations of GSK2269557 may be presented by treatment arm or pooled where appropriate. Full details of all statistical analyses will be pre specified in the RAP prior to unfreezing of the database.

Rationale 1

To date GSK2269557 has been developed as a lactose-blended powder delivered by oral inhalational via the DISKUS device. However, it is planned to commercialize GSK2269557 using the ELLIPTA device and to include magnesium stearate as a stabiliser. Therefore, the production of GSK2269557 in the DISKUS device will be discontinued and all future studies, including the current study, will be conducted/completed using the ELLIPTA device. Any patient currently participating in or enrolled in the study prior to approval of a protocol supporting the switch to the ELLIPTA device will complete the study with the DISKUS device. Patients enrolled after approval of the latter, will start and complete the study with the ELLIPTA device. The dose selected and approved in the current DISKUS device is 1000 µg, with the equivalent dose in the ELLIPTA being 700µg.

Change 2:

Include patients with APDS1 with new disease-associated mutations and APDS2 with mutations in the PIK3R1 regulatory subunit of class IA phosphoinositide 3 kinases.

Throughout the protocol: Change “Type 1 APDS/PASLI” to “Type 1 or 2 APDS/PASLI”

Page 10, Section 1. Protocol Synopsis for study 204745 (Rationale) and Page 14, Section 2.1. Study Rationale:

GSK2269557 in addition to standard of care, in patients with activated phosphoinositide 3-kinase delta syndrome **1**/p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (APDS**1**/PASLI-**CD**) **and activated phosphoinositide 3-kinase delta syndrome 2/p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (APDS2/PASLI-R1)**.

Page 14, Section 2.2. Brief Background:

APDS**1 (PASLI-CD)** is a rare (prevalence estimated to be <1/1,000,000), combined primary immune deficiency syndrome caused by a dominant gain-of-function heterozygous mutation in p110δ, the catalytic subunit of phosphoinositide 3-kinase δ (PI3Kδ). **A number of** ~~Currently there are four described~~ mutations **e.g.** E1021K, N334K, E525K and C416R, with E1021K the most common [Angulo, 2013; Lucas, 2014] **have been described**. Clinically, APDS is characterized by recurrent respiratory infections with *Streptococcus pneumoniae* and *Haemophilus influenzae*, causing structural lung damage (small airways disease and bronchiectasis). In addition, some patients experience severe infections with Herpes-group viruses, and there is an increased risk of B cell malignancy [Lear, 2014]. Typically, disease in APDS patients is difficult to manage, with the use of prophylactic antibiotic and antiviral agents, i.v. antibiotics, and immunoglobulin replacement being the mainstay of treatment. The limited treatment options available to these patients' means early death from infection-related causes remains a prominent feature of the disease [Lear, 2014]. **Recently, APDS 2 (PASLI-R1), a primary immunodeficiency resulting from autosomal dominant gain-of-function mutations in PI3KR1, the gene coding for the regulatory subunit of class PI3Ks, has been described. The clinical, immunological and histopathological features of APDS2 are similar to those described in APDS1 patients [Elkaim, 2016, Olbrich, 2016].**

Page 29/30, Section 5.1. Inclusion Criteria

2. Patients with a clinical phenotype consistent with APDS, including a history of recurrent (frequency greater than would be expected in an immunocompetent individual) ear, sinus or pulmonary infections, and who have a known type 1 APDS-associated genetic PI3Kδ mutation (**e.g**. E1021K, N334K, E525K and C416R) **or type 2 APDS-associated mutation**

Rationale 2

Following review of the clinical characteristics, biology and histopathological features of APDS type 2 or PASLI-R1, it is clear that this is similar to that in patients with APDS type 1 or PASLI-CD and therefore it is anticipated that any effect of GSK2269557 would be similar in both disease types. Therefore, it is considered appropriate to include patients with APDS type 2 into this study.

Change 3:

Administrative changes:

Page 2, Summary of Protocol Amendment 01 (item 15)

15. Proposed analyses of BAL updated to indicate that proteomic analysis will be performed on the **lavage supernatant** ~~Epithelial Lining Fluid~~ *not* the cell pellet

Page 10, Objectives and Endpoints and page 17, Section 3.0., Objectives and Endpoints:

In BAL cell pellet/ ~~ELF~~ ***lavage supernatant*** *when available, analysis of:*

- Lymphocyte cell subsets
- Exploratory phospho-protein biomarkers (e.g. pAKT)
- Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9)
- Exploratory mRNA biomarkers
- Proteomic markers **(lavage supernatant only)**
- Antibody levels

Page 15, Section 2.2., Brief Background

- ***Study 201544 (healthy volunteers):*** **single centre, three part, randomised, study to evaluate the safety, tolerability and pharmacokinetics of GSK2269557 administered via the ELLIPTAdry powder inhaler to healthy subjects (study completed but not yet reported).**

GSK2269557 was well tolerated across the range of doses tested.

GSK2269557 has been administered to stable COPD patients in study PII115119:

- ***Study PII115119 (stable COPD patients):*** **daily doses of up to 2000 µg GSK2269557 are being administered via the DISKUS DPI for 14 days.**

There are also ~~four~~ **three** ongoing studies (not reported), ~~three~~ **two** in COPD patients and one in asthma patients:

- ~~*Study PII115119 (stable COPD patients):* daily doses of up to 2000 µg GSK2269557 are being administered via the DISKUS DPI for 14 days.~~

Page 35, Section 5.4., Withdrawal/Stopping Criteria

Subjects withdrawn from study treatment will also be withdrawn from the study. **Subjects who are withdrawn should complete the assessments planned for the early withdrawal visit within 2 weeks of withdrawal (see Table 5).** The subject will **also** receive a follow-up telephone call within 1−2 weeks after the last dose of study medication**, if the early withdrawal visit was conducted during the first week following withdrawal** ~~(see Table 5).~~ The reason for withdrawal will be recorded in the case report form (CRF)

Page 45, Section 7.1., Time and Events Table (Table 5)

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early with-drawal **(within 2 wks)**	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days					
In-Patient	X	X	X										
Out-Patient				X		X	X	X	X	X		X	
Telephone Contact/ Research nurse visit					X weekly						X		Except weeks where subjects have a clinic visit
SAFETY ASSESSMENTS													
Brief physical exam	X			X		X	X	X		X		X	Pre-dose
AE/SAE review	←==========→										X	X	
Concomitant medication review	←==========→										X	X	
Vital signs	X	X		X		X	X	X	X	X		X	Pre-dose. Single assessment
12-lead ECG	X	X		X		X	X	X		X		X	Pre-dose. Single assessment
Urine pregnancy test	X			X			X	X		X			only WCBP
Laboratory assessments (include haematology, biochemistry, Urinalysis)	X			X		X	X	X		X		X	Pre-dose
STUDY TREATMENT													
~~DISKUS~~ **ELLIPTA** inhaler ~~demonstration and practice~~ **training**	X												**Review of the Patient Information Leaflet with the subject (no device will be used). Additional training may be conducted at the discretion of the investigator**

Rationale 3

Clarifications, corrections of typographical errors and inconsistencies.

AMENDMENT 3

List of Specific Changes and Rationale (Bold text depicts new text while strike through text depicts deleted text)

Change 1:

Replace the administration of nemiralisib in a blend containing 0.6% MgSt, via a dry powder ELLIPTA inhaler (700 µg) by a comparable dose nemiralisib in a blend containing 0.4% magnesium stearate (MgSt) administered via the ELLIPTA device (500 µg).

Throughout the protocol: change "700 µg" to "500 µg" of nemiralisib.

Section 4.5. Dose Justification:

The formulation of Nemiralisib has been changed to the current formulation of nemiralisib with lactose monohydrate/0.4% Magnesium Stearate (MgSt) which is the proposed final formulation and currently being investigated in the dose ranging study. The previous formulation currently used in the study is blended with lactose and 0.6% MgSt). The reduction in concentration of MgSt in the new formulation has resulted in a change in the respirable mass of the drug product and hence a reduction in dose is possible. The blend containing 0.4% MgSt is considered the final formulation and intended for progression into Phase III and favours a lower total doses of drug for further development.

The dose chosen for this study is ~~7~~**5**00 µg of ~~GSK2269557~~**nemiralisib** per day administered via a dry powder ELLIPTA inhaler **containing 0.4% MgSt** for a duration of up to 84 days (-4/+2 days) and is expected to be equivalent to a dose of **either 700 µg nemiralisib blended with 0.6% MgSt administered via the ELLIPTA DPI or the** 1000 µg administered via DISKUS in terms of the dose deposited and retained within the lungs based on PK parameters (AUC and $C_{~~trough~~max}$). **The delivered dose and deposition profile to the lungs is a function of the device and formulation which is reflected in the observed data (plasma pharmacokinetics) for all the formulations. Data and plasma exposures have been generated (completed or ongoing studies) in human for these different devices and formulations (up to 2000 µg in DISKUS once daily for 14 days in PII116617; 700 µg in ELLIPTA DPI (0.6% MgSt formulation) once daily for 10 days in 205759 and 750 µg in ELLIPTA DPI (0.4% MgSt formulation) once daily for 3 months in the ongoing 2b study 200879 in exacerbating COPD patients). A recent healthy volunteer trial using the ELLIPTA DPI 0.4% MgSt formulation has been compared (using plasma exposure following 500 µg) with the data generated for each device and formulation in terms of the observed trough (24 hours post dose) concentrations and these are shown in the following table.**

Table 01: Observed plasma concentrations on Day 1 at trough (24 hours post dose) in healthy volunteers following inhaled Nemiralisib administration by device/material

Study	Device/Material	Population	Dose (µg)	Plasma Ctrough (24 hrs post Day 1 dose) pg/mL	
				Geometric mean	95% CI
PII116617	DISKUS	HVT	1000*	196	167-230
205759	ELLIPTA DPI 0.6%MgSt	HVT - Japanese	700	239	180-316
207674^	ELLIPTA DPI 0.4%MgSt	HVT	500	166	120-228

*** Extrapolated from 2000 µg (Ctrough at 24h of 392 pg/mL and 90% confidence interval of 334-460) dose level since 1000 µg was not a dose level in study PII116617**
^ Preliminary data from a completed but unreported trial 207674

The selected 500 ug dose is expected to achieve a similar level of inhibition of PI3Kδ within the lungs during the treatment phase of this study on a once a day regimen as the 700 µg administered via ELLIPTA DPI (0.6% MgSt formulation) or 1000 µg administered via DISKUS. This dose has been selected based on previous safety and tolerability data in humans **including** ~~(~~healthy subjects, healthy smokers and COPD patients including exacerbating patients following ~~GSK2269557~~**nemiralisib** administration via a DISKUS DPI, and healthy subjects via ELLIPTA DPI~~)~~, as well as pharmacokinetics and demonstration of target (PI3Kδ) inhibition by observed changes in biomarkers. This will be the first time ~~GSK2269557~~**nemiralisib** is dosed to patients who have been identified as having APDS, and it is assumed that these patients will have a similar lung deposition, distribution and plasma exposure to healthy volunteers and COPD patients**.** ~~(who had similar exposure). Twice the proposed dose (2000 µg in DISKUS) using the same formulation has previously been given once daily to~~ **No differences between populations of** healthy ~~male smokers for 14 days (study PII116617)~~**volunteers** and ~~to stable COPD patients (study PII115119). A total daily dose of 1000 µg is currently being studied in exacerbating COPD patients for 3 months (study PII116678 and study 201928) and patients with persistent, uncontrolled asthma for 28 days (study 201543).~~ **patient groups has been observed in inhaled systemic plasma exposure parameters in studies to date.**

The nature of the mutation in APDS 1 and 2 patients causes a modification in the catalytic and regulatory subunits of PI3Kδ respectively leading to a lower activation threshold of the enzyme and hence a faster rate of PIP_2 conversion, higher levels of PIP_3, and by implication, localised immune-suppression and a predisposition to infection and subsequent tissue damage [Angulo, 2013, Elkaim, 2016]. ~~GSK2269557~~**Nemiralisib** is a competitive antagonist preventing ATP driven PIP_2 conversion and is therefore expected to achieve similar levels of PI3Kδ enzyme inhibition in APDS patients to those seen in healthy subjects, but lead to an overall greater reduction in PIP_3.

The target site of action for inhaled PI3Kδ inhibition is the intracellular compartment of immune cells resident in lung tissue and lumen. ~~GSK2269557~~**Nemiralisib** has a high

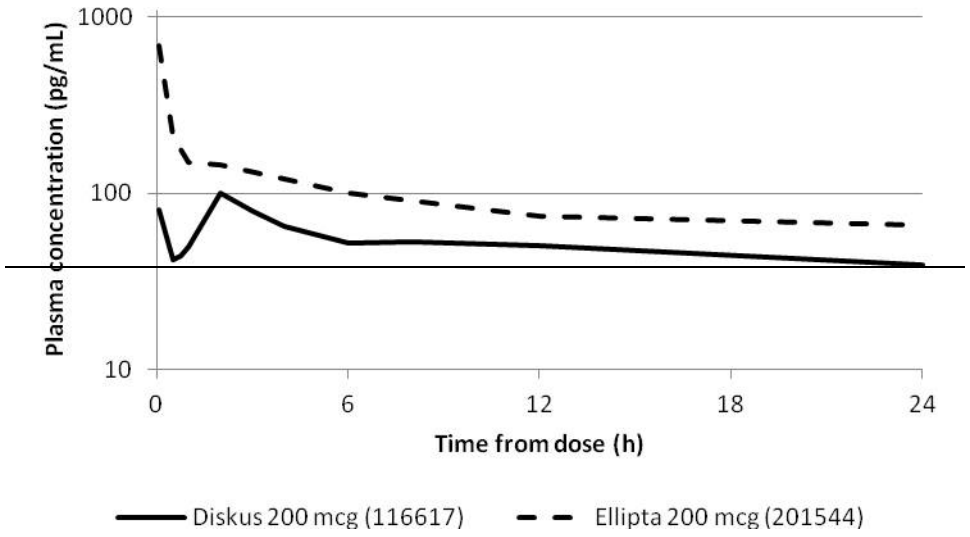
potency and selectivity at the PI3Kδ enzyme (Ki value 0.1 ng/mL). The pathophysiology of APDS is not fully understood, but is believed to involve a significant neutrophil component as well as T/B-cell and leukocyte driven effects. The predicted steady-state intracellular concentration of ~~GSK2269557~~**nemiralisib** at trough (24h) in the lungs of APDS patients is ~~about~~**approximately** 1~~83~~**56** ng/mL (3.~~8~~**3** ng/mL free drug) following ~~10~~**05**00 µg ~~DISKUS~~**ELLIPTA** DPI **0.4% MgSt formulation**, implying PI3Kδ inhibition in excess of 80% throughout the ~~inter-~~dosing interval in all cell types of interest. Systemic **exposure** and tissue concentrations are predicted to be extremely low (Cmax of ~~1.8~~**4.5** ng/mL, 0.0~~4~~**9** ng/mL free drug), implying very little PI3Kδ inhibition ~~(<30%)~~ outside of the lung.

~~During the development of GSK2269557 as a dry powder for inhalation a switch has been made both in terms of device (to ELLIPTA) as well as formulation (addition of magnesium stearate as a formulation stabiliser). PK data has been used to calculate an equivalent 1000 µg dose from DISKUS in the ELLIPTA delivered drug product. Plasma PK data obtained from study 201544 with ELLIPTA DPI (part B, 200 µg OD for 14 days) (study completed but report not yet available) showed about 35% increase in systemic exposure compared to the steady state exposure of GSK2269557 following DISKUS DPI in study PII116617, Under the assumption that the ratio of intracellular concentration of GSK2269557 at trough in the lungs of APDS patients and plasma concentration stays the same, it is expected that 700 µg ELLIPTA DPI will produce similar PI3Kδ inhibitions in the lungs as that with 1000 µg DISKUS DPI.~~

~~Figure 2 shows the single dose day 1 median concentration time data derived from study 201544 when healthy volunteers were dosed with 200 µg via the ELLIPTA device together with the data for DISKUS derived from study PII116617 (extrapolated down from the 500 µg data). The 35% difference can clearly be seen in particular in the latter time points. The 35% increase in exposure (AUC and C_{trough}) is reflective of an observed increase in respirable mass as measured by *in vitro* drug product performance (Aerodynamic Particle Size Distribution). In addition to the overall increase in respirable mass there is a change in the distribution within the respirable mass fraction, with the magnesium stearate formulation of the ELLIPTA DPI producing a higher level of very fine particles. The approximate 350% increase seen in the C_{max} is believed to be reflective of this difference in distribution. The very fine particles are predicted to be deposited more to the alveolar region and hence absorbed more rapidly therefore contributing to the initial C_{max}. It is assumed that the increase in C_{trough} is reflective of the additional drug being deposited in the peripheral compartment (in this case the effect compartment of the resident cells of the lung) and it's therefore this measure which has defined the appropriate comparator to compare the two devices to match effect compartment exposure response.~~

~~The increased C_{max} in the ELLIPTA device would result in a median Day 1 concentration of approx 1.4 ng/mL achieving approximately 3.1 ng/mL at steady-state (> Day 6) which would still result in a low level of systemic pharmacology at peak of approximately 23 or 39% inhibition respectively whilst maintaining pharmacology (≥ 80%) in the lungs. However these peak levels are likely to drop off rapidly in plasma as can be seen in figure2.~~

Figure 2 Median Plasma Concentrations Post Single Inhaled Dose in Healthy Volunteers Following Dosing via Either DISKUS or ELLIPTA



Pharmacodynamic assessments conducted during the trial will monitor target engagement and downstream effects to be measured with a view to confirming the PKPD relationships in these APDS patients.

Any patient participating in this study prior to approval of the protocol supporting the switch to the ELLIPTA DPI (0.4% MgSt) will complete the study with the ELLIPTA DPI (0.6% MgSt). Patients enrolled after approval of the ELLIPTA device (0.4% MgSt) will start and complete the study with the ELLIPTA DPI (0.4% MgSt).

Section 6.1. Investigational Product and Other Study Treatment:

Product name:	~~**GSK2269557**~~**Nemiralisib ELLIPTA DPI (500 μg)**	~~**GSK2269557 ELLIPTA DPI (100 μg)**~~
Formulation description:	~~GSK2269557~~**Nemiralisib** blended with lactose and magnesium stearate in ELLIPTA DPI	~~GSK2269557 blended with lactose and magnesium stearate in ELLIPTA DPI~~
Dosage form:	Dry powder for inhalation	~~Dry powder for inhalation~~
Unit dose strength:	500 μg / blister	~~100 μg / blister~~
Route of Administration	Inhalation	~~Inhalation~~
Dosing instructions:	Inhale **ONCE in the MORNING** as directed	~~Inhale as directed~~

Section 6.2. Treatment Assignment

The study is an open-label design.

All subjects will be assigned ~~GSK2269557~~**nemiralisib** ~~7~~**5**00 µg once daily.

A new randomisation will be produced to accommodate the inclusion of a ~~second~~**third** treatment arm into the study. This is to allow for the reporting of the data to be performed on a treatment level where appropriate.

Section 6.9. Treatment of Study Treatment Overdose

For this study, any dose of ~~GSK2269557~~**nemiralisib** > 1**4**00 µg within a 24 hour time period ± 2 hours will be considered an overdose.

Section 7.8. 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~~.

Section 9.3.2. Primary Analyses

The t~~wo~~**hree** formulations of ~~GSK2269557~~**nemiralisib** may be presented by treatment arm or pooled where appropriate. Full details of all statistical analyses will be pre-specified in the RAP prior to unfreezing of the database.

Rationale 1:

The formulation of Nemiralisib has been changed to the current formulation of nemiralisib with lactose monohydrate/0.4% Magnesium Stearate (MgSt) which is the proposed final formulation. Any patient participating in this study prior to approval of the protocol supporting the switch to the ELLIPTA DPI (0.4% MgSt) will complete the study with the ELLIPTA DPI (0.6% MgSt). Patients enrolled after approval of the ELLIPTA device (0.4% MgSt) will start and complete the study with the ELLIPTA DPI (0.4% MgSt).

Change 2:

Exploratory Phamacodynamics endpoint Volatile Organic Chemicals (VOCs) analysis in breath removed.

Section 1 PROTOCOL SYNOPSIS FOR STUDY 204745 and Section 3 OBJECTIVE(S) AND ENDPOINT(S)

Exploratory	
Pharmacodynamics: To understand lung disease biology in patients with APDS and to explore the pharmacodynamic effects of inhaled ~~GSK2269557~~**nemiralisib**.	Endpoints may include, but are not limited to: ***In blood and sputum, analysis of:*** • Cellular PIP3 peak area as a proportion of (PIP3 peak area + PIP2 peak area) • Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) • Immune cell subsets • Exploratory phospho-protein biomarkers (e.g. pAKT) • Exploratory messenger ribonucleic acid (mRNA) biomarkers ***In BAL cell pellet/* lavage supernatant *when available, analysis of:*** Lymphocyte cell subsets Exploratory phospho-protein biomarkers (e.g. pAKT) Soluble proinflammatory mediators (including IL-8, IL-6, TNFα & MMP9) Exploratory mRNA biomarkers Proteomic markers (lavage supernatant only) Antibody levels ***In blood, analysis of:*** Bacterial DNA fragments ~~***In breath, analysis of:***~~ • ~~Volatile organic chemicals (VOCs)~~

Section 7 STUDY ASSESSMENTS AND PROCEDURES

If assessments are scheduled for the same nominal time, THEN the assessments *should* occur in the following order:

1. physical examinations
2. vital signs
3. 12-lead ECG
4. lung function tests (spirometry)
5. blood draws
6. pregnancy test
7. ~~volatile organic compounds (VOCs)~~
8. sputum induction

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

Section 7.1. Time and Events Table

Procedure	Pre-Screening	Screening (up to 42 days prior to dosing)	Clinic visit #1 At least 7 days prior to dosing	Notes
~~Breath sample for VOC analysis~~		~~X~~	~~X~~	~~Only performed if capabilities exist at the study site to take samples of breath condensate.~~

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early withdrawal (within 2 wks)	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days	-4 / +2 days			±2 weeks	
~~Breath sample for VOC analysis~~	~~X~~			~~X~~		~~X~~	~~X~~	~~X~~		~~X~~		~~X~~	~~Pre-dose. Only performed if capabilities exist at the study site to take samples of breath condensate.~~

Section 7.6.1. Volatile organic chemicals (VOCs) in breath

~~Section 7.6.1. Volatile organic chemicals (VOCs) in breath~~

~~If capabilities exist at the study site, samples of breath condensate will be taken for assessment of VOCs following treatment with GSK2269557, at the time points indicated in the Time Events Table [Section 7.1].~~

~~Subjects will be asked to refrain from drinking alcohol or applying cosmetics on the day of the test.~~

~~Subjects will wear a tight-fitting mask supplied with air and with a sample tube attached, and breathe normally until 5 L of exhaled breath are collected through the sample tube.~~

~~For further information on collection, processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).~~

Section 9.3.2.1. Exploratory Biomarker Analyses

The results of exploratory biomarker investigations (e.g. ~~VOC in breath and~~ bacterial DNA fragment analysis) may be reported separately from the main clinical study report.

All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Rational 2:

Exploratory Phamacodynamics endpoint Volatile Organic Chemicals (VOCs) analysis in breath removed as capabilities not available at study site.

Change 3:

Risk assessment table updated with post inhalation cough.

Section 4.6.1. Risk Assessment

Post-inhalation cough immediately following inhalation of study treatment (nemiralisib)	**In the Proof-of-Concept (PoC) study PII116678, which was conducted in 126 randomized participants from a population similar to this protocol and a previous formulation of nemiralisib (DISKUS formulation blended with only one excipient, lactose), there was a higher incidence of treatment-related, mild and moderate adverse events of cough (Preferred Term) reported immediately after dosing in exacerbating subjects in the nemiralisib DISKUS 1000 mcg QD group (n=22 [35%] compared exacerbating subjects in the placebo DISKUS group (n=2 [3%]). For the 22 subjects in the nemiralisib 1000 mcg group, the events for 20 of the subjects were considered by the Investigator to be related to study treatment. From the**	**The ICF will inform participants that in previous clinical trials, post-inhalation cough has been reported following nemiralisib administration and that the post-inhalation cough is considered related to nemiralisib.** **In addition, participants will be able to record any AE's (including events of post-inhalation cough) in the diary card provided (See Section 7.8).**

	review of reported terms, cough often occurred immediately after dosing and in some subjects it seemed to repeat on most of the dosing days. **Cough was reported to be generally mild or moderate and resolved after stopping dosing. Three subjects (all in the nemiralisib DISKUS 1000 mcg QD group) discontinued the study due to cough. Additional details are provided in the Nemiralisib (GSK2269557) Investigator's Brochure.**	

Rational 3:

In previous clinical trials, post-inhalation cough has been reported following nemiralisib administration. Post-inhalation cough is considered related to nemiralisib and therefore added as a potential risk.

Change 4:

Change to inclusion criteria 3 the lower limit BMI cut off to 17 kg/m2 and the lower limit for weight to 40kg.

Section 5.1. Inclusion Criteria

WEIGHT
3. Body weight ≥4~~5~~**0** kg and body mass index (BMI) ≥1~~8~~**7** kg/m^2 (inclusive)

Rational 4:

APDS patients have a longstanding chronic condition and so are more likely to fall outside the normal range for BMI. Therefore adoption of a slightly lower BMI for this patient group is considered appropriate and safe.

Change 5:

Change to inclusion criteria 4. The requirement for additional contraception for males with partners of child bearing potential has been removed.

Section 4.6.1. Risk Assessment

Unknown risks to an embryo, fetus or nursing infant	There are no studies with ~~GSK2269557~~**nemiralisib** in pregnant or lactating women.	As specified in the protocol: • Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate. Female subjects must be postmenopausal or using a highly effective contraception method to avoid pregnancy while in this study. • If a female subject becomes pregnant during the study, she must let the study doctor know immediately. The study medication will be stopped. • For women of reproductive potential, a pregnancy test will be performed at Screening, on Day 1 and Day 28 and at the Follow-up Visit. ~~• Male subjects with female partners of reproductive potential must use highly effective contraception methods to avoid pregnancy while in this study.~~

Section 5.1. Inclusion Criteria

SEX
4. ~~**Male subject.** 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 completion of the follow-up telephone call at 1-2 weeks from last dose.~~ ~~Vasectomy with documentation of azoospermia.~~ ~~Male condom plus partner use of one of the contraceptive options below:~~ ~~• Contraceptive subdermal implant~~ ~~• Intrauterine device or intrauterine system~~

SEX
~~• Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]~~ ~~• Injectable progestogen [Hatcher, 2011]~~ ~~• Contraceptive vaginal ring [Hatcher, 2011]~~ ~~• Percutaneous contraceptive patches [Hatcher, 2011]~~ ~~This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by ICH [ICH M3 (R2), 2009].~~ ~~The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.~~

Section 7.3.2. Pregnancy

Details of all pregnancies in female subjects ~~and if indicated female partners of male subjects~~ will be collected after the start of dosing and until the 3 months follow-up visit.

Details of pregnancies for female partners of male participants will not be routinely collected; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism.

Section 12.5.2. Collection of Pregnancy Information

Male participants with partners who become pregnant

- **Investigator will not routinely attempt to collect pregnancy information on any male participant's female partner(s) who becomes pregnant while the male participant is participating in this study; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism. •If pregnancy information for a male participant's female partner(s) is voluntarily reported, after obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.**
- **Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK**
- **Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.**

~~• 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.~~

Rational 5:

Based on the predicted margins for semen exposure on findings across the reproductive toxicology studies range between 29811 and 192452 fold, which are well above the threshold for concern, and the absence of genotoxic effects in cellular assays, the requirement for additional contraception for males with partners of child bearing potential has been removed. Details of pregnancies for female partners of male participants will not be routinely collected; however, voluntary reports of such incidents will be captured through the GSK standard reporting mechanism.

Change 6:

Change to exclusion criteria 5 concomitant medication.

Section 4.6.2. Benefit Assessment

- All subjects will continue (with changes, where needed, to antimicrobial treatment that are not strong cytochrome (CYP)3A4~~/CYP2D6~~ inhibitors) to receive established standard of care

Section 5.2. Exclusion Criteria

CONCOMITANT MEDICATIONS
~~5. Regular or chronic treatment with strong inhibitors of CYP3A4 and/or CYP2D6 (this includes some anti-epileptic treatments, macrolide antibiotics, oral antifungal treatments and anti-tuberculosis therapy (see Section 6.12.2) are prohibited from the screening visit until the end of treatment visit. Where clinically appropriate, an alternative drug in the same class (or unrelated class) that is not a strong CYP3A4 and/or CYP2D6 inhibitor can, after signing informed consent, be substituted for the original strong inhibitor of these enzymes.~~**CYTOCHROME P450 3A4:** **Strong CYP3A4 substrates:** **Strong inhibitors of cytochrome P450 3A4: Currently, only limited in vivo**

information is available on the in vivo metabolism of nemiralisib; and, the role of cytochrome P450s (CYPs) in the elimination of nemiralisib is based upon in vitro data. In vitro studies indicate that nemiralisib is predominantly metabolised by CYP3A4 enzymes with minor contributions from CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2J2. Co-administration of nemiralisib with CYP3A4 inhibitors may result in increased systemic exposure to nemiralisib. Regular or chronic treatment with medications that are considered strong inhibitors of CYP3A4 are not permitted:

- **Antiretrovirals including protease inhibitors (e.g., indinavir, nelfinavir,ritonavir, saquinavir, atazanavir)**
- **Oral antifungal treatments such as ketoconazole and itraconazole. Short courses of up to 14 days are allowed for fluconazole and voriconazole, but chronic administrations are not permitted. It is recommended that amphotericin or posaconazole are used as oral antifungal treatment of choice.**
- **Antibiotics such as telithromycin and troleandomycin (macrolide). Short courses up to 14 days are allowed for mibefradil (calcium channel blocker), erythromycin and clarithromycin (including intravenous clarithromycin) but chronic administrations are not permitted. Azithromycin may be used chronically and is recommended as the macrolide antibiotic of choice.**
- **Anti-epileptic treatments; and anti-tuberculous therapy.**

These medications must all have been stopped at least 14 days prior to first dose of study treatment.

Sensitive narrow therapeutic index CYP3A4 substrates:
Nemiralisib is a time-dependent inhibitor of CYP3A4 and co-administration of CYP3A4 substrates with nemiralisib may result in increased systemic exposure to the CYP3A4 substrate. Regular or chronic treatment with medications that are considered sensitive narrow therapeutic index substrates of CYP3A4 are, therefore, not permitted:

- **Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine and tacrolimus.**

These medications must all have been stopped at least 14 days prior to first dose of study treatment.

- **Intravenous and oral theophylline will be allowed according to the approved label/Prescribing Information, since a specific mechanistic model constructed for nemiralisib co-administered with theophylline, suggests a negligible effect of nemiralisib on theophylline exposure. Monitoring of patients receiving IV theophylline will be required in line with normal practice.**

~~6.~~ • Use of unstable dosing regimen with i.v. Ig / s.c. Ig in the last 6 months before screening. Stable maintenance immunoglobulin regimen, as per local practice, such as regular injections with a consistent dosing interval (e.g. monthly) is acceptable.

~~7.~~ • Previous use of an mTOR antagonist (e.g. rapamycin, everolimus) or PI3K delta inhibitor (selective or non-selective PI3K inhibitors) **within 6 weeks prior to first dosing.**

Section 5.4.3. Other Safety Stopping Criteria

- If during the study, a strong inhibitor of CYP3A4 ~~and/or CYP2D6~~ is prescribed, the study drug should be stopped for the duration of the treatment with the strong inhibitor and not restarted for at least two-weeks after the strong inhibitor has been stopped. In the event that the co-prescribed drug cannot be stopped, the study drug should be permanently stopped and the patient withdrawn from the study.

Section 6.12.2. Prohibited Medications and Non-Drug Therapies

Concomitant use of inhibitors of CYP3A4 substrates is not permitted. Acute administration (up to 14-day dosing) of some of the 3A4 inhibitors is, however, permitted. See Section 6.2 Exclusion Criteria 5 for detail. ~~Regular or chronic treatment with strong inhibitors of CYP3A4 and/or CYP2D6 (this includes some anti-epileptic treatments, macrolide antibiotics, oral antifungal treatments, and anti-tuberculosis therapy (Table) are prohibited from the screening visit until the end of treatment visit.~~ Where clinically appropriate, an alternative drug in the same class (or unrelated class) that is not a strong CYP3A4 ~~and/or CYP2D6~~ inhibitor can, after signing informed consent, be substituted for the original strong inhibitor of these enzymes **(Table 4).** If during the study, a strong inhibitor of CYP3A4 ~~and/or CYP2D6~~ is prescribed, the study drug should be stopped for the duration of the treatment with the strong inhibitor and not restarted for at least two-weeks after the strong inhibitor has been stopped. In the event that the co-prescribed drug cannot be stopped, the study drug should be permanently stopped and the patient withdrawn from the study (see Section 5.4.3).

Table ~~3~~4 Inhibitors of CYP3A4~~/CYP2D6~~ substrates and alternatives

Class of Drug	CYP3A4 Inhibitors	Possible Alternative(s)
Macrolide antibiotics	clarithromycin	azithromycin ~~erythromycin~~
	troleandomycin	
	telithromycin	
	erythromycin	
Antifungal	itraconazole	~~Fluconazole~~ amphotericin **posaconazole**
	ketoconazole	
	~~posaconazole~~	
	voriconazole	
	fluconazole	

Anti-retroviral (PI)	indinavir	Tipranavir. Other classes e.g. NNRT
	lopinavir/ritonavir	
	nelfinavir	
	ritonavir	
	saquinavir	
	atazanavir	
Anti-HCV (PI)	boceprevir	Other classes e.g. Ribavirin, Peginterferon alfa
	telaprevir	
Non-selective CaChB	mibrefradil*	amlodipine
Non-peptide ADH inhibitor	conivaptan	
Anti-HT2 Antidepressant	nefazodone*	Other classes
~~*withdrawn~~		
~~Class of Drug~~	~~CYP2D6~~	~~Alternatives~~
SSRI Anti-depressants	fluoxetine	fluvoxamine
	paroxetine	Other classes
Class IA Anti-arrythmic	quinidine	
Smoking cessation	buproprion	NRT
Immunosuppressant	**cyclosporine**	
	rapamycin	
	tacrolimus	
	everolimus	
Ergot alkaloid	**ergotamine**	
	dihydroergotamine	
Opioid	**fentanyl**	

	alfentanil	
Antipsychotic	**pimozide**	

Rational 6:

Adjusted in line with latest drug interaction data. Information about interaction with inhibitors of CYP3A4 substrates has been added for consistency since this has also been implemented for the most recent studies.

Change 7:

Dose reduction removed.

Section 6.4. Subject Specific Dose Adjustment Criteria

In the event of adverse events, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator and/or medical monitor to dosing with ~~GSK2269557~~**nemiralisib**, treatment will be halted and safety review of the subject will be undertaken. ~~Following relevant reporting and discussion with the GSK Medical Monitor and relevant GSK personnel, consideration may be given to reducing the dose of GSK2269557 to 500 µg O.D.~~

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 at the study 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~~ ~~(~~**the** counter reading after completing dose administration~~)~~ will be recorded. Compliance will be checked by the site staff at each planned visit.

A record of the number of ELLIPTA DPIs dispensed to each subject and the number of actuations administered, read from the dose counter for each ELLIPTA DPI, 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.

Rational 7:

Dose reduction removed as dose strength is 500µg / blister, therefore dose reduction will no longer be an option.

Change 8:

Time and Event schedule visit window added to Follow Up Visit.

Section 7.1. Time and Events Table

Procedure	Treatment Period										Follow-up Period		Notes
Clinic Visit	2			3		4	5	6		Early with-drawal (within 2 wks)	1-2 wks and 4-6 wks	7	
Day	-1	1	2	14	2 to 84	28	56	83	84‡			3 mths	
Visit window	N/A	N/A	N/A	±2 days	±3 days	-4 / +2 days	-4 / +2 days	-4 / +2 days	-4 / +2 days			±2 weeks	

Rational 8:

To provide clearer instruction with regard to time windows

Change 9:

Administrative changes, including change from the compound number GSK2269557 to the INN nemiralisib, corrections, relevant updates, including reporting time frame of pregnancy information and clarifications also made.

Throughout the protocol: change "GSK2269557 µg" to "nemiralisib".

Medical Monitor/Sponsor Information Page updated

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	~~Fax Number~~	Site Address
Primary Medical Monitor	PPD	PPD	PPD	PPD	~~GSK, Stockley Park West 1-3 Ironbridge Road, Middlesex, UB11 1BT, UK~~**GSK, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK**

Secondary Medical Monitor	PPD	PPD	PPD	PPD	GSK, Stockley Park West 1-3 Ironbridge Road, Middlesex, UB11 1BT, UK

Section 2.2. Brief Background

- *Study 201544 (healthy volunteers):* single centre, three part, randomised, study to evaluate the safety, tolerability and pharmacokinetics of ~~GSK2269557~~**nemiralisib** administered via the ELLIPTA™ dry powder inhaler ~~to healthy subjects (study completed but not yet reported)~~**(0.6% MgSt formulation) – single doses up to 200 µg, and daily doses of 200 µg for 10 days.**
- **Study 205759 (*healthy Japanese volunteers*): single and repeat doses of nemiralisib administered via the ELLIPTA™ DPI (0.6% MgSt formulation) – single doses up to 700 µg, and daily doses up to 700 µg for 10 days.**
- **Study 207674 (*healthy volunteers*): single dose of nemiralisib 750 µg or a single dose of 500 µg administered via the ELLIPTA™ DPI (0.4% MgSt formulation) (study completed but not yet reported).**
- **Study 206764 (*healthy volunteers*): An open-label study in healthy male subjects, to determine the excretion balance and pharmacokinetics of [14C]-GSK2269557, administered as a single intravenous micro-tracer (concomitant with an inhaled non-radiolabelled dose) and a single oral dose (study completed but not yet reported).**
- **Study 206874 (*healthy volunteers*): one sequence cross over study (nemiralisib 100 µg (via the ELLIPTA™ DPI (0.4% MgSt formulation) alone followed by nemiralisib 100 µg co-administered with itraconazole). A study to evaluate the effect of itraconazole on the PK of nemiralisib (study completed but not yet reported)**

~~GSK2269557~~**Nemiralisib** was well tolerated across the range of doses tested.

~~GSK2269557~~**Nemiralisib** has been administered to ~~stable~~COPD patients in **the following** stud~~y~~**ies**~~PII115119~~:

- *Study PII115119 (stable COPD patients):* daily doses of up to 2000 µg ~~GSK2269557~~**nemiralisib** ~~are being~~ administered via the DISKUS™ DPI for 14 days.
- **Study PII116678 (patients experiencing a COPD exacerbation): daily doses of 1000 µg nemiralisib administered via the DISKUS™ DPI for 12 weeks.**

Nemiralisib has been administered to patients with persistent, uncontrolled asthma:

- **Study 201543 (*patients with persistent, uncontrolled asthma*): daily doses of 1000 µg nemiralisib are being administered via the DISKUS™ DPI for 28 days**

There are also t~~hree~~**wo** ongoing studies (not reported)~~, two~~ in COPD patients~~and one in asthma patients~~:

- ~~*Study PII116678 (patients experiencing a COPD exacerbation):* daily doses of 1000 µg GSK2269557 are being administered via the DISKUS DPI for 12 weeks.~~
- *Study 201928 (patients experiencing a COPD exacerbation):* daily doses of ~~1000~~**700** µg ~~GSK2269557~~**nemiralisib** ~~are~~ being administered via the ~~DISKUS~~**ELLIPTA™** DPI **(0.6% MgSt formulation)** for 12 weeks.
- ~~*Study 201543 (patients with persistent, uncontrolled asthma):* daily doses of 1000 µg GSK2269557 are being administered via the DISKUS DPI for 28 days~~
- **Study 200879 (*patients experiencing an acute COPD exacerbation*): daily doses up to 750µg nemiralisib administered via the ELLIPTA™ DPI (0.4% MgSt formulation) for 84 days in a dose ranging study**

Section 1 PROTOCOL SYNOPSIS FOR STUDY 204745 and Section 4.1. Overall Design

This is a ~~multi~~**single**-centre, open-label, uncontrolled, single group, study in patients with APDS 1 and 2.

Eligible subjects will be enrolled in the study and receive ~~GSK2269557~~**nemiralisib** ~~7~~**5**00 µg once daily for 84**3** days (-4/+2 days).

Section 1 PROTOCOL SYNOPSIS FOR STUDY 204745 and Section 4.2. Treatment Arms and Duration

- Subjects will then dose at home for the remainder of the treatment period (with the exception of clinic visit days, when they will dose in the study clinic). On Day 14 ± 2, Day 28 (-4/+2 days), Day 56 (-4/+2 days), **Day 83 (-4/+2 days)** and Day 84 (-4/+2 days) **(optional sub-study patients only)**, subjects will return to the study clinic on an outpatient basis, in order to complete the assessments described in the Time & Event table (Section 7.1).

Section 4.4. Design Justification

Treatment period	~~• 12 weeks is the maximum dosing period possible with the pre-clinical safety data available.~~ • **Safety:** The safety aim of this study is to assess any frequent, safety events which deviate from prior safety data.

	The 12-week treatment period builds on significant prior data collected in healthy volunteers**,** ~~and~~ COPD **and asthma** patients where ~~GSK2269557~~**nemiralisib** has been well tolerated up to 12 weeks treatment. No drug-related serious adverse event(s) (SAEs) have been observed to date. The most common AEs to date are **post-inhalation** cough and headache. • **PK:** ~~GSK2269557~~**Nemiralisib** reaches steady state after 5-7 days repeat dosing. Assessing **plasma** PK at day 14 & 83 will enable the assessment of a sustained level of ~~GSK2269557~~**nemiralisib exposure** in this patient cohort. • **PD:** Changes in a range of PD markers have been measured during studies in patients with COPD, following 2 weeks dosing with ~~GSK2269557~~**nemiralisib**.

Section 7.1. Time and Events Table

‡ Day 84 visit will only occur if a subject has agreed to take part in the BAL sub-study, **dosing will continue until the D84 visit.**

Section 7.7.3. Patient Exit Interview

This assessment will be completed by all study participants **and may be held** at ~~all~~**the** study clinic~~s~~ **or the subject's home.** The exit interview will be conducted, transcribed and analysed in English as outlined in the Interview Discussion Guide.

Section 12.5.2. Collection of Pregnancy Information

• Information will be recorded on the appropriate form and submitted to GSK within ~~2 weeks~~24 hours of learning of a subject's pregnancy.

Rational 9:

Administrative changes, relevant updates and clarifications.