TITLE PAGE

Protocol Title: A Phase IIb, Randomized (Stratified), Double-Blind (Sponsor Open), Parallel-Group, Placebo-Controlled, Dose-Finding Study of Nemiralisib (GSK2269557) Added to Standard of Care (SoC) Versus SoC Alone in Participants Diagnosed with an Acute Moderate or Severe Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Protocol Number: 200879/ Amendment 02

Short Title: A Phase IIb, Placebo-Controlled, Dose-Finding Study of Nemiralisib (GSK2269557) Added to Standard of Care (SoC) Versus SoC Alone in Participants Diagnosed with an Acute Moderate or Severe Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Compound Number: GSK2269557

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Regulatory Agency Identifying Number(s): FDA IND Number:125676; EudraCT #: 2017-001074-42

Approval Date: 14-DEC-2017

SPONSOR SIGNATORY:

PPD

14 - DECEMBER - 2017

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document	Date
Amendment02 – Global Amendment *(Document Number* 2017N317218_05)	*14-DECEMBER-2017*
Amendment 01 – Country Amendment – Korea *(Document Number 2017N317218_04)*	*26-SEPTEMBER-2017*
Amendment 01 – Global Amendment *(Non-tracked changes version: document number 2017N317218_03 – to re-insert the missing text shown in bold that was present in the tracked changes version of Amendment 1 (document number 2017N317218_01), but inadvertently missing from the non-tracked changes version of Amendment 1(document number 2017N317218_02) for Exclusion Criterion #6: "6. Other respiratory disorders: A diagnosis of α1-antitrypsin deficiency as the underlying cause of COPD, active tuberculosis, lung cancer, clinically overt* ***bronchiectasis (Note: focal bronchiectasis is not exclusionary), sarcoidosis,*** *pulmonary fibrosis (Note: focal fibrotic pulmonary lesions are not exclusionary), primary pulmonary hypertension, interstitial lung diseases, or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the subject or affect the interpretation of the results."*	*26-SEPTEMBER-2017*
Amendment 01 – Global Amendment *(Non-tracked changes version: document number 2017N317218_02)*	*15-SEPTEMBER-2017*
Amendment 01 – Global Amendment *(Tracked changes version: document number 2017N317218_01)*	*24-AUGUST-2017*
Original Protocol *(document number 2017N317218_00)*	*15-JUNE-2017*

Amendment 02 14-DEC-2017

Overall Rationale for the Amendment: The rationale for this amendment is to add an additional lower strength(s) of nemiralisib, to remove the restrictions on theophylline use, to adjust withdrawal from study and discontinuation of treatment criteria, to adjust the flow for participants that discontinue IP, to remove the recording of SAEs between signing of informed consent form and start of study treatment, and to provide clarification of local and central lab requirements. Additionally, inconsistencies in protocol amendment 1 were corrected and wording was clarified where necessary.

This protocol amendment applies to all participating Investigators globally.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Study Rationale, Study Schematic, Section 5.2, 7.1, 7.2, 10.1, 10.2,	12.5mcg dose strength has been added and anticipated participant numbers in each dose arm adjusted accordingly. Provision for 25mcg to be included at a later date has also been added. Randomisation ratio has been updated to add the 12.5mcg dose strength and to allow for the 25mcg dose strength. Explanation for this change has been added where appropriate and wording related to the planning of this change has been removed.	Additional lower dose strengths have been added to fully profile the dose response. This was planned in the original protocol
Section 6.2, Exclusion 20	Exclusion criteria related to QTc adjusted to permit triplicate ECGs as opposed to single ECGs for assessment of QTc interval criteria.	Adjusted in line with permissible GSK safety requirements.
Section 6.2, Exclusion 13, Appendix 10	Exclusion 13 adjusted to clarify wording and to remove the restriction of theophylline. Associated Appendix 10 removed	Theophylline can be used in accordance with standard practicein light of emerging drug:drug interaction data.
Section 6.2, Exclusion 16, Section 7.7	Exclusion 16 removed and wording in Permitted Medication section clarified	Discussion between respiratory and sleep experts indicate that if participants are on a stable dose of CPAP or NIPPV that started prior to screening this is acceptable and won't interfere with efficacy endpoints.
Section 8.1, 8.2	The following events were moved from the Withdrawal From Study section to the Discontinuation of Study Treatment section: Pneumonia Acute Respiratory Acidosis/invasive mechanical ventilation Significant changes to ECG, Vital signs, Lab tests. Pregnancy	None of these events require withdrawal from study. Participants that discontinue IP due to these events may remain in the study.
Section 9.2.1	Time period for collection of SAES has been adjusted to only collect SAEs between ICF and start of study treatment if they are assessed to be related to study participation, or related to a GSK product.	Collection of ALL SAEs between the signing of ICF and start of study treatment was agreed to be unnecessary. The requirement has reverted to the GSK standard for the time period for collection of SAEs.
SoA, Section 8.1	Study flow adjusted so that participants that discontinue	Adjusted in recognition of the fact that 12 weeks of post

Section # and Name	Description of Change	Brief Rationale
	study treatment move directly into the 12-week post treatment follow up period rather than continuing for the remainder of the 12-week treatment period.	treatment follow up is sufficient for participants who discontinue study treatment.
Synopsis, Overall Design, Section 3.1, 5.1, 5.5, 7.1	Clarification provided that dosing at V2 can be performed up to 3pm, extended from 12midday in the previous protocol.	Extended in recognition that there a large number of assessments to be performed and Visits 1 and 2 prior to dosing. Accumulation of drug is observed in the repeat dose pharmacokinetics of nemiralisib of approximately at least 2-fold and therefore dosing up until 3:00 pm on Day 1 does not pose a risk of overdosing on Day 2 when the Day 2 dose is administered in the morning (as early as 6:00 am [i.e., approximately 15 hours after the previous day's dose])
Section 6.2, Exclusion 9, Section 9	Exclusion 9 clarified to allow randomisation ahead of receipt of virology results, with participants to be withdrawn if subsequently found to be positive. Other sections updated to further explain this	Turnaround time of virology is greater than the 48h screening window
Synopsis, Study Rationale, Section 5.1, 7.1	Start of SoC was defined	This was not clear previously
Section 7.1, Section 9	Clarified throughout that the time of randomisation is anchored to the start of SoC (i.e. 48hrs from start of SoC)	This was clarified because some sections anchored time of randomisation to completing screening assessments whilst other anchored time of randomisation to start of SoC which was difficult to interpret/manage.
SoA, Section 9.1	Confirmation added that V1 and V2 can be combined and clarification given on what assessments to be done if V1 and V2 combined	Clarified following feedback from investigators
SoA	Removed requirement for Laboratory assessments at V2	Recognition that only one laboratory assessment is required prior to randomisation.
3.3 Benefit/Risk Assessment	Information about interaction with inhibitors of CYP304 inhibitors and CYP3A4 substrates has been added	This risk was omitted previously

Section # and Name	Description of Change	Brief Rationale
3.3 Benefit/Risk Assessment	Risk of patient s performing spirometry during a moderate or severe exacerbation has been added	Highlighted as a risk by Investigators. Benefit:Risk assessment remains unchanged.
Synopsis, Section 5.1, 7.2, Appendix 3	Required membership of the iSRC has been adjusted.	Independent clinician with experience in respiratory and general medicine was agreed to be adequate by the safety group in place of a respiratory clinician and a cardiologist.
SoA	SoA updated to add IRT visit at Week 3	Previously omitted in error
Section 5.1	Definition of moderate and severe exacerbations added in Section 5.1 for clarity	Previously this was only in the appendix which could have been overlooked
Section 6.3.4	Clarification that if participants are unable to withhold their usual scheduled COPD medications on the day of a clinic visit the visit may still take place.	This was added to recognise the fact that some patients may not be able to withhold their usual COPD medications if experiencing an exacerbation.
Section 7.1	Clarification provided that treatment of subsequent exacerbations during the study do not need to follow the SoC definition for the Index exacerbation	Clarified following feedback by investigators
SoA, Section 7.6	The requirement to enter dose counter information, and date and time of each dose administered in the clinic into the eCRF in countries where the propeller health sensor is used has been added	Previously omitted in error
Section 7.7	Reference to prohibited CYP3A4 inhibitors and narrow therapeutic index substrates added here directing the reader to Exclusion no. 13	Added so that important prohibited medication information is not missed.
Section 9	Central lab volumes updated in line with central lab specifications	Precise central lab volumes were not available at writing of the protocol
Section 9	Clarification added that local laboratory results must be received prior to randomisation to allow review of Exclusion 9 and 18	This was not previously clear.
Section 9.1	Reminder added to the section on spirometry that rescue medication and usual daily COPD medications should be withheld on the moring of spirometry assessments	Added because this is an important element of the spirometry assessment.

Section # and Name	Description of Change	Brief Rationale
Section 9.1	Clarification added that the first EXACT-PRO will be completed in the morning whilst for the remainder of the study it will be performed in the evening.	This is because it is important that at randomisation the EXACT-PRO is completed before any other assessments are completed.
Section 9.2.7, Appendix 9	The section relating to DREs was simplified as previous wording was not clear. Appendix 9 was updated in line with this.	To clarify how and when to record exacerbations, which are considered DREs, in the eCRF
Section 9.3	Text regarding the treatment of overdose was adjusted	To ensure that definition of an overdose and required actions are clear and appropriate for a double-blind study.
Section 9.4.1	Clarification added around when a complete physical exam is required and when a brief physical exam is required	Previously this was not documented in the protocol.
Section 9.4.2	Timing of vital signs was adjusted	Previously it was not consistent with other sections.
Section 9.4.3	Paragraph referring to other QT correction formula has been removed	Previously this was inconsistent with other paragraphs/sections
Section9.4.3	Clarification added that a local ECG can be used to assess eligibility criteria however a central ECG must be performed at screening	This was implicit previously and so has ben mad explicit following feedback from investigators
Section 9.4.4, Appendix 2	Use of local labs at screening has been made mandatory	This is because the turnaround time of safety labs results from the central lab is longer than the 48hr screening window.
Section 9.4.4	Requirement to record non protocol specified local labs in the eCRF has been removed	There is no facility in the eCRF to record local labs
Seciton 10.2	Definition of All Patients Enrolled (APE) Population redefined	To define a more appropriate APE population in line with the RAP
Appendix 9	Further information provided for the definition of Severe COPD exacerbation	Clarified following feedback from Investigators
Various Sections	Repetition of information was removed from various sections	To simplify the protocol

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1. SYNOPSIS

Protocol Title: A Phase IIb, Randomized (Stratified), Double-Blind (Sponsor Open), Parallel-Group, Placebo-Controlled, Dose-Finding Study of Nemiralisib (GSK2269557) Added to Standard of Care (SoC) Versus SoC Alone in Participants Diagnosed with an Acute Moderate or Severe Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Short Title: A Dose-Finding Study of Nemiralisib (GSK2269557) Added to Standard of Care (SoC) Versus SoC Alone in Participants Diagnosed with an Acute Moderate or Severe Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

Rationale:

GSK2269557 (hereafter referred to according to the generic name 'nemiralisib,' with the exception of reference to a previous study[ies] that used an earlier formulation of GSK2269557) is a potent and highly selective inhaled Phosphoinositide 3-Kinase Delta (PI3Kd) inhibitor being developed as an anti-inflammatory for the treatment of inflammatory airways disease. To date, nemiralisib has been administered to participants with an acute exacerbation of chronic obstructive pulmonary disease (COPD), asthma, and to healthy volunteers (both smokers and former smokers).

This study will be undertaken in COPD participants diagnosed with an acute moderate or severe exacerbation of COPD requiring treatment with SoC. Standard of Care (SoC) for the index exacerbation is defined for this protocol as treatment with oral/systemic corticosteroid(s) (prednisone 40 mg/day or equivalent) for 5 days **and** antibiotic[s] for 7 days; the dose and/or duration of prednisone (40 mg or equivalent) and/or the antibiotic can be modified according to the Investigator's/medically qualified designee's judgement or according to local country/institution practice. The start of SoC is defined as the start of either oral/systemic corticosteroids[s] or antibiotic[s] whichever is earliest.

Participants will be treated with nemiralisib or placebo in addition to SoC. The study is designed to assess the dose response, efficacy, safety, and pharmacokinetics of nemiralisib across a range of doses (up to 750 mcg) compared with placebo for 12 weeks, with an additional 12-week post-treatment follow-up period. The range of doses to be evaluated in this study should be sufficient to enable full characterization of the dose response curve of nemiralisib, with respect to the primary endpoint (change from baseline in Clinic Visit trough forced expiratory volume in one second [FEV_1] measured post-bronchodilator at Day 84). This study is also designed to estimate the rate reduction of re-exacerbations on a selected dose of nemiralisib compared with placebo.

The information obtained from study 200879 will be used to select the optimally effective and safe dose of nemiralisib for further COPD studies. In addition, this study will evaluate and confirm the pharmacokinetic (PK) profile of nemiralisib within a subset of the patient population.

Objectives and Endpoints:

Objective	Endpoint
Primary	
To characterize the dose response of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	Change from baseline in Clinic Visit trough FEV_1 at Day 84 measured post-bronchodilator Baseline is defined as the post-bronchodilator FEV_1 measured prior to the first dose of double-blind study treatment on Day 1.
Secondary	
• To characterize the dose response, and efficacy, of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of moderate and severe exacerbations over the 12-Week Treatment Period • Time to next moderate/severe exacerbation following index exacerbation. • Change from baseline in clinic visit trough FEV_1 measured pre and post-bronchodilator at Days 14, 28, 56, and 84 (Day 84: post-bronchodilator is the primary endpoint; pre-bronchodilator is a secondary endpoint) and at hospital discharge (only for participants who are hospitalized for the index exacerbation) • Change from hospital discharge in clinic visit trough FEV_1 measured pre- and post-bronchodilator at Days, 14, 28, 56, and 84 (in participants hospitalized for index exacerbation only)
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptoms indicative of an exacerbation and on health status using Patient-Reported Outcomes (PROs) in participants diagnosed with an acute moderate or severe exacerbation of COPD	<u>EXAcerbations of Chronic Pulmonary Disease Tool (EXACT-PRO)</u> • Proportion of participants achieving the EXACT definition of recovery from the index exacerbation by Days 14, 28, 56, and 84 • Time to recovery from index exacerbation • Severity of subsequent Health Care Resource Utilization (HCRU)-defined moderate and severe exacerbation(s) defined by EXACT

Objective	Endpoint
	COPD Assessment Test (CAT) • Proportion of responders using the CAT at Treatment Days 28, 56, and 84, and following EXACT defined recovery from the index exacerbation • Change from baseline (Day 1) in CAT total score at Days 28, 56, and 84 and following EXACT defined recovery from the index exacerbation St. George's Respiratory Questionnaire (SGRQ) Total Score • Proportion of responders on the SGRQ total score as measured by the SGRQ for COPD Patients (SGRQ-C) at Days 28, 56, and 84 • Change from baseline (Day 1) in SGRQ total score at Days 28, 56, and 84
• To evaluate the usage of rescue medication in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rescue medication use (occasions/day), averaged over each week of treatment and over the 84-day treatment period. • The percentage of rescue-free days (24-hour periods) during each week of treatment and over the 84-day treatment period
• To evaluate the population pharmacokinetics of nemiralisib in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Plasma nemiralisib concentrations and derived PK parameters (e.g., area under the curve [AUC (0-24) and AUC(0-t)], maximum concentration [Cmax], time at maximum concentration [Tmax], Ctrough) as appropriate will be collected in a subset of randomized participants (approximately 300) at selected sites as follows: trough (pre-dose) for the study treatment and post-dose for the study treatment from 0-1 hour and >1 hour to 6 hours on Days 14 and 28 of the 12-Week Treatment Period
• To assess the safety and tolerability of nemiralisib and placebo in participants diagnosed with an acute moderate or	• Incidence of adverse events (AEs; including serious AEs and AE of Special Interest

Objective	Endpoint
severe exacerbation of COPD	[AESI]) • Vital signs (pulse rate, systolic and diastolic blood pressure) (measured at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • 12-lead electrocardiogram (ECG) assessments (performed at clinic Visits 1 [Screening], 3 [Day 14], 6 [Day 84], and 7 [Day 112] or Early Withdrawal Visit) • Clinical laboratory tests (hematology and chemistry; performed at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • Incidence of COPD exacerbations
Exploratory – 12-Week Treatment Period • To further characterize the dose response, and efficacy, of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of mild exacerbations over the 12-Week Treatment Period • Rate of all exacerbations (mild, moderate and severe combined) over the 12-Week Treatment Period • Time to next exacerbation (mild, moderate and severe combined)
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptom stability following an exacerbation using Patient-Reported Outcomes in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Stability of symptoms post recovery measured using E-RS:COPD (Evaluating Respiratory Symptoms in COPD) and subscales from Randomization (Visit 2) to Day 84 (Visit 6)
• To explore the PK/PD relationship for nemiralisib	
• To evaluate the treatment effect of nemiralisib in addition to SoC compared	• Relationship between drug exposure and Pharmacodynamic responses (e.g. efficacy, heart rate, clinical laboratory analytes and blood biomakers) in the PK subset of participants (approximately 300) at selected sites.

Objective	Endpoint
with placebo and SoC on HCRU in participants who experience a severe exacerbation of COPD	• Measures of HCRU related to severe exacerbations (e.g., hospitalizations, length of hospital stay, re-hospitalization within 30 days, number of Emergency Room [ER] visits, etc.)
• To evaluate the compliance with study treatment	• Number of actuations of the double-blind study treatment as measured by the clip-on Propeller Sensor (for countries where the Propeller Sensor for ELLIPTA is available)
• To evaluate inflammatory markers in blood in relation to acute exacerbation of COPD	• Blood samples collected at Screening through Visit 7 (as part of the clinical laboratory blood samples) for analysis of blood eosinophil counts and inflammatory mediators • Blood samples for analysis of inflammatory biomarkers (including but not limited to: high sensitivity C-reactive protein [hs-CRP], chemokine interferon-γ inducible protein 10 kDa (CXCL10)], and procalcitonin) collected at Visit 1 (Screening)
• To evaluate inflammatory and infective markers in sputum in relation to acute exacerbation of COPD	• Spontaneous sputum sample for analysis of inflammatory and infective markers collected at Screening/Day 1 (pre-dose) and Day 56 in participants who are willing and able to provide a sample

Objective	Endpoint
Exploratory – Post-Treatment Follow-Up Period To evaluate the potential post-treatment impact of double-blind study medication during the 12-Week Post-Treatment Follow-Up Period	• Change from baseline (Day 84) in Clinic Visit trough FEV_1 measured pre- and post-bronchodilator at Day 112, 140, and 168 • Rate of moderate and severe COPD exacerbation(s) during the 12-Week Follow-Up Period • Rate of moderate and severe COPD exacerbation(s) over the 24-week study duration • Time to next exacerbation following cessation of double-blind study treatment • Proportion of responders using the CAT at Days 112 and 168 • Change from baseline (Day 1) in CAT Total score at Days 112 and 168 • Proportion of responders on the SGRQ Total Score as measured by the SGRQ-C at Days 112 and 168 • Change from baseline (Day 1) in SGRQ total score at Days 112 and 168 • Severity of subsequent HCRU exacerbation defined by EXACT • E-RS: COPD and subscales from last dose of double-blind treatment • Rescue medication use up to Day 112

Overall Design:

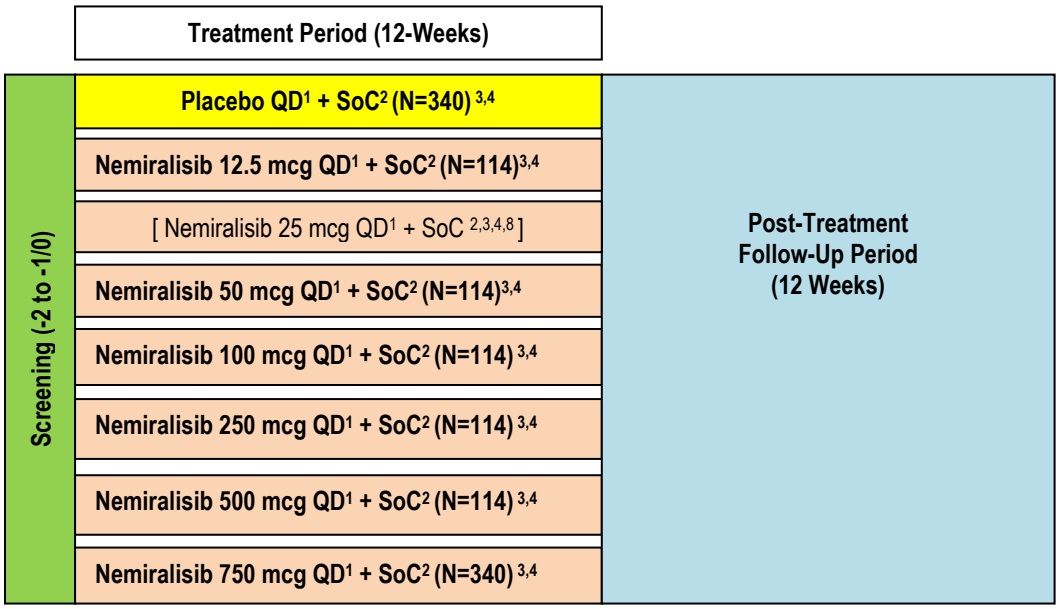
This is a Phase IIb, multicenter, randomized, stratified, double-blind (Sponsor Open), placebo-controlled, parallel-group study in participants who present with an acute moderate or severe exacerbation of COPD requiring SoC. Standard of Care (SoC) for the index exacerbation is defined for this protocol as treatment with oral/systemic corticosteroid[s] (prednisone 40 mg/day or equivalent) for 5 days **and** antibiotic[s] for 7 days; the dose and/or duration of prednisone (40 mg/day or equivalent) and/or the antibiotic can be modified according to the Investigator's/medically qualified designee's judgement or according to local country/institution practice. The start of SoC is defined as the start of either oral/systemic corticosteroids[s] or antibiotic[s] whichever is earliest. In addition to double-blind study treatment and SoC treatment for the COPD

exacerbation, other treatment(s) for the exacerbation (i.e., bronchodilators) and regular COPD maintenance therapy are permitted.

This study consists of a Screening Period, a 12-Week Treatment Period and a 12-Week Post-Treatment Follow-Up Period. Participants will visit the hospital (participants who are hospitalized for the index exacerbation of COPD)/clinic a minimum of eight (if Screening and Randomization visit combined) to nine times over a 24-week period as shown in the Study Schematic below. Randomization and the first dose of the double-blind study treatment administration (Visit 2/Day 1) should take place in the morning, as soon as possible following determination of eligibility and completion of the baseline PRO measures, including the EXACT-PRO questionnaire for the day of randomization, and FEV_1 measurement and no later than 48hrs after the start of SoC.

Note: In the event that completion of the assessments/procedures at Visit 2 (or in cases where Visit 1 and Visit 2 are conducted on the same day) extends past noon, the first dose of the double-blind study treatment administration may occur up until 3:00 pm on Day 1. After Day 1, dosing should take place in the morning each day through the end of the 12-Week Double-Blind Treatment Period. The total duration of study participation is approximately 6 months (170 days).

Study Schematic



Clinic Visit:	1	2[5]	3	4	5	6[6]	7	8	9[7]
Day:	-2 to -1	1	14 (±3)	28 (±3)	56 (-4/+3)	84(-4/+3)	112 (-4/+3)	140 (-4/+3)	168 (-4/+3)

QD=once daily; SoC=Standard of Care

1. Inhalation Powder administered once-daily in the morning via the ELLIPTA inhaler
2. For this study, SoC for the index exacerbation is defined for this protocol as treatment of the COPD exacerbation with oral/systemic corticosteroid[s] (prednisone 40 mg/day or equivalent) for 5 days **and** antibiotic[s] for 7 days; the dose and/or duration of prednisone (or equivalent) and/or the antibiotic can be modified according to local

country/institution practice. The start of SoC is defined as the start of either oral/systemic corticosteroids[s] or antibiotic[s] whichever is earliest
3. Note: subjects may receive additional treatment[s] for the exacerbation (e.g., bronchodilator) and will be on a background of regular COPD maintenance therapy
4. These figures are approximate and assume that no further adjustments to the randomization ratio are made. The actual sample sizes at the end of the study may be different, depending upon whether changes are made following the results of the unblinded interim analysis which may modify the planned allocation.
5. Randomization and first dose of double-blind (Sponsor Open) study treatment
6. End of Treatment Period (last dose of double-blind [Sponsor Open] study treatment)
7. Last day of study
8. The option to add a dose strength of 25 mcg following the results of an unblinded interim analysis has been included if further characterization of the lower end of the dose response curve is required

PK Subgroup: Sparse PK sampling will be conducted at selected sites. The PK Subgroup will be identical to the main study in terms of the study population, design, and conduct, with the exception of blood draws (3 per visit on Days 14 and 28) for PK analysis.

An internal Safety Review Committee (iSRC) will have study oversight to ensure that it meets the highest standards of ethics and participant safety and to carry out the planned interim safety data analyses/data reviews. Data will be reviewed by the iSRC on a periodic basis, as defined in the iSRC Charter. The iSRC, which will comprise a minimum of 3 people (including an independent statistician, and an independent clinician with experience in respiratory and general medicine), will be authorized to review unblinded interim safety analyses/data during the study.

Number of Participants:

Approximately 1,667 participants will be screened (assumes an approximate 25% Screen Failure rate) to achieve approximately 1,250 randomized participants who present with an acute moderate or severe exacerbation of COPD, such that approximately 1,000 participants (assumes an approximate 20% withdrawal rate) complete the 12-Week Treatment Period. Randomization will be stratified by index COPD exacerbation severity (moderate or severe) and by whether or not that participant is in the PK Subgroup, to ensure a balance across treatments within each strata. The plan is to randomize approximately 340 participants each to the placebo and nemiralisib 750 mcg groups and approximately 570 participants across the other nemiralisib groups. The reason for inflating the sample size for a selected dose of nemiralisib (planned as the 750 mcg dose) and the placebo group is for the aim to increase precision around the pair-wise comparison between them for the key secondary objective of the reduction in the rate of re-exacerbations.

Treatment Groups and Duration:

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

This study consists of a Screening Period, a 12-Week Treatment Period and a 12-Week Post-Treatment Follow-Up Period. Participants will visit the hospital/clinic a minimum of eight to nine times over a 24-week period as shown in the Study Schematic above. Following determination of eligibility, participants will be randomized into the study at Visit 2 (Randomization/Day 1). The total duration of study participation is approximately 6 months (170 days).

Participants will be required to participate in the following:

Screening (-2 to -1/0 Days Prior to Visit 2 [Randomization/Day 1]): Following diagnosis of an acute moderate/severe exacerbation of COPD during outpatient assessment by the Investigator, or designated physician, or during an Emergency Department visit or acute admission to hospital:

1. The start of the SoC for the index exacerbation is defined as the start of either oral/systemic corticosteroids[s] or antibiotic[s] whichever is earliest and is expected to start shortly after diagnosis, though it may already have been started before formal diagnosis of COPD exacerbation. If SoC is started >48 hours prior to diagnosis, the participant is not eligible to participate, but may be re-screened in the future as described in the main protocol.

2. All Screening/baseline assessments should be completed within 48hrs of start of SoC.

12-Week Double-Blind Treatment Period: Once-daily study treatment administration will start on Day 1 (Visit 2).

At the end of the Screening Period (-2 to -1/0 days), participants who meet all of the Inclusion Criteria and none of the Exclusion Criteria will complete Visit 2 (Randomization Visit/Day 1). If a participant meets all of the eligibility criteria, it is possible for him/her to complete the Screening Visit and the Randomization Visit on the same day (e.g., outpatient participant who presents with an acute moderate exacerbation of COPD).

At this visit, participants will be randomized to receive one of the doses of nemiralisib QD or placebo QD in addition to SoC for 12 weeks.

Randomization and the first dose of the double-blind study treatment administration should take place in the morning, as soon as possible following determination of eligibility and completion of the baseline PRO measures, including the EXACT-PRO questionnaire for the day of randomization, and FEV_1 measurement and no later than 48hrs after the start of SoC.

Note: In the event that completion of the assessments/procedures at Visit 2 (or in cases where Visit 1 and Visit 2 are conducted on the same day) extends past noon, the first dose of the double-blind study treatment administration may occur up until 3:00 pm on Day 1. After Day 1, dosing should take place in the morning each day through the end of the 12-Week Double-Blind Treatment Period.

Participants will be permitted to continue taking inhaled maintenance COPD medications (e.g., long-acting bronchodilators, long-acting beta$_2$-agonist/corticosteroid combinations, long-acting muscarinic antagonist/long-acting bronchodilator combinations, etc.). Study-supplied rescue medication (albuterol [salbutamol] metered-dose inhaler [MDI] or nebules) for treatment of acute symptoms of COPD will also be permitted. Other concomitant medications, may be allowed at the discretion of the GSK Medical Monitor and/or Investigator

Participants will then dose at home each morning until Day 84 (– 4 / + 3 days), with the exception of the days when participants come to the clinic. On those days, they will dose at the clinic.

During the 12-week Treatment Period, participants will return to the clinic on an outpatient basis for Visits 3-6 on Study Days 14 (± 3 day), 28 (± 3 days), 56 (– 4 / + 3 days) and 84 (– 4 / + 3 days) to complete the assessments described in the Schedule of Assessments.

Participants who withdraw from the study before completing the 12-week Treatment Period will be asked to return to the clinic within 24 hours (or as soon as possible) for end of treatment assessments (Early Withdrawal Visit).

If a participant is withdrawn from study treatment, he/she will continue existing maintenance COPD therapy or will be prescribed appropriate treatment for COPD and will move directly to the 12-Week Post-Treatment Follow-Up Period for collection of data starting with Visit 7, 28 days after the discontinuation of study treatment.

12-Week Post-Treatment Follow-up Period: The 12-week period following the last dose of double-blind study treatment.

During the 12-week Post-Treatment Follow-Up Period, participants will return to the clinic on an outpatient basis for Visits 7-9 on Study Days 112 (– 4 / + 3 days), 140 (– 4 / + 3 days), and 168 (– 4 / + 3 days) to complete the assessments described in the Schedule of Assessments.

Participants who withdraw from the study before completing the 12-week Post-Treatment Follow-Up Period will be asked to return to the clinic within 24 hours (or as soon as possible) for end of study assessments (Early Withdrawal Visit).

Interim analyses may be performed, recruitment rate permitting, to potentially adapt the randomization ratio across the doses to help characterize the dose response profile of FEV_1, to stop the study for futility, to assess the initial study assumptions and to change the proportions for the stratification of index exacerbation by severity (moderate or severe).

Also, depending upon the findings of the iSRC reviews (See Appendix 3), participants in this protocol will continue to be randomized according to the current randomization schedule (i.e., 3:1:1:1:1:1:3) or randomization to a given study treatment arm(s) may be reduced/halted and the randomization allocation for the given study treatment arm(s) may

be re-allocated to another study treatment arm(s). A dose strength of nemiralisib 25 mcg may be added following the results of an unblinded interim analysis if further characterization of the lower end of the dose response curve is required.

2. SCHEDULE OF ACTIVITIES (SOA)

12-Week Double-Blind Treatment Period

Procedure	**Screening**	**Double-Blind Treatment Period**					**Early Withdrawal**
Visit	1	2	3	4	5	6	Early Withdrawal
Day	-2 to -1	1 (Randomization)[1]	14	28	56	84	
Visit window		N/A	± 3 days	±3 days	- 4/+3 days	- 4/+3 days	
Informed consent	X						
PGx informed consent	X						
Demography	X						
Medical history (includes COPD history, COPD exacerbation history, substance usage and family history of premature CV disease	X						
Chest X-Ray (or CT scan)	X						
Past and current medical conditions (including cardiovascular medical history and therapy history)	X						
Register visit in IRT	X	X	X	X	X		
EFFICACY ASSESSMENTS							
Dispense eDiary and initiate training module within		X					
Review eDiary		←==========	==========	==========	==========	==========	==========→
Collect eDiary							X
EXACT[2]		←==========	==========	==========	==========	==========	==========→
CAT[3]		X		X	X	X	X
SGRQ-C[4]		X		X	X	X	X
COPD exacerbation assessment		X	X	X	X	X	X
Clinic Visit FEV_1		X[5,6]	X[5]	X[5]	X[5]	X[5]	X

Procedure	**Screening**	**Double-Blind Treatment Period**					**Early Withdrawal**
Visit	1	2	3	4	5	6	Early Withdrawal
Day	-2 to -1	1 (Randomization)[1]	14	28	56	84	
Visit window		N/A	± 3 days	±3 days	- 4/+3 days	- 4/+3 days	
SAFETY ASSESSMENTS							
AE/SAE review		←==========					→
Double-blind study treatment tolerability assessment (within 5 minutes immediately following dosing)		X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X
Physical exam, including height and weight	X	X	X	X	X	X	X
Vital signs	X	X[7]	X[7]	X[7]	X[7]	X[7]	X
12-lead ECG	X[8]		X[7,8]			X[7,8]	X[8]
Laboratory assessments (including hematology and biochemisty)	X[9]		X[7]	X[7]	X[7]	X[7]	X
Hep B and Hep C screen	X[10]						
HIV screen	X[10]						
Serum pregnancy test (only WOCBP)	X						
Urine pregnancy test (only WOCBP)				X[11]	X[11]	X[11]	X[11]
BIOMARKERS/GENETICS/SPUTUM/PHARMACOKINETICS							
Blood sample for biomarker analysis	X[12]			X[12]		X[12]	
Genetic sample		X[13,14]					
Spontaneous sputum sample	X[15]				X[15]		
Serial blood samples for PK analysis (selected sites only)			X[13,16]	X[13,16]			
OTHER							
Review smoking status	X	X	X	X	X	X	X

Procedure	**Screening**	**Double-Blind Treatment Period**					**Early Withdrawal**
Visit	1	2	3	4	5	6	Early Withdrawal
Day	-2 to -1	1 (Randomization)[1]	14	28	56	84	
Visit window		N/A	± 3 days	±3 days	- 4/+3 days	- 4/+3 days	
Smoking cessation counselling	X	X	X	X	X	X	X
Health Care Resource Utilization (HCRU) Review		←==========→					
STUDY TREATMENT/RESCUE MEDICATION							
Inhaler and Propeller Sensor training		X[17]					
Randomization		X[18]					
Double-blind study drug administration[18]		←==========→					
Assessment of study treatment compliance			X[19]	X[19]	X[19]	X[19]	X[19]
Rescue medication use[20]		←==========→					

AM=morning; CAT=COPD Assessment Test; CV=cardiovascular; EXACT=EXAcerbations of Chronic Pulmonary Disease Tool; FEV_1=forced expiratory volume in one second; HIV=Human Immunodeficiency Virus; IRT=Interactive Response Technology; PGx=pharmacogentics research; PK=pharmacokinetic; WOCBP=women of child-bearing potential

1. If a participant meets all of the Inclusion Criteria and none of the Exclusion Criteria, it is possible for him/her to complete the Screening Visit and the Randomization Visit on the same day (e.g., outpatient participant who presents with an acute moderate exacerbation of COPD). In this case, the following assessments/procedures only need to be conducted once: concomitant medication assessment, physical exam, vital signs (including height and weight), and review of smoking status and smoking cessation counselling.
2. Subjects should complete the EXACT as follows: Visit 2: Completed during the Visit (prior to completing other study assessments/procedures); thereafter: completed daily in the evening
3. Subjects should complete the CAT at the visits noted as well as 7 days post EXACT-defined day of recovery after index exacerbation (for the latter, the CAT will be triggered to appear in the e-Dairy on the evening following confirmation of recovery from an EXACT-defined event).; the CAT will be completed prior to the SGRQ-C and other study assessments/procedures
4. Subjects should complete the SGRQ-C after completing the CAT and prior to other study assessments/ procedures
5. Spirometry will be performed in the morning (i.e., initiated between 6:00AM and 12:00PM) prior to the first dose of double-blind study treatment (Day 1)/ pre-dose at trough (approximately 24 hours following the previous morning's dose of double-blind study treatment [all other visits]) at two time points each: pre-bronchodilator and post-bronchodilator (approximately 10 to 30 minutes following treatment with albuterol [salbutamol], administered as either four inhalations via the metered-dose inhaler [MDI] (i.e., 400 mcg) with valved-holding chamber or one nebulized treatment)
6. For participants hospitalized for the index exacerbation at Screening, spirometry (as noted in the bullet above) should also be performed in the morning on the day of discharge
7. Pre-dose
8. Single assessment

9. Screening: Due to the short screening window, local laboratory results will be used for purposes of determining subject eligibility for randomization. If local laboratory results are already available within 48 hours from diagnosis of the index COPD exacerbation, these results can be used for determination of subject eligibility; there is no need to take another sample for local analysis. A sample for central laboratory analysis should also be obtained.
10. Presence of hepatitis B surface antigen (HBsAg) and/or positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment or positive test for HIV antibody is exclusionary. NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study treatment is exclusionary. NOTE: Hepatitis C RNA test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing. Because of the short window for Screening, double-blind study treatment may start before the results of the hepatitis and HIV tests have been received. If subsequently the test(s) is(are) found to be positive, the participant will need to be withdrawn from study treatment and may also be withdrawn from the study as judged by the Principal Investigator in consultation with the Medical Monitor.
11. If the urine pregnancy text result is positive, a blood sample for serum pregnancy testing will need to be conducted to confirm pregnancy status
12. Approximately 20 mL (4 teaspoons) of blood will be collected in all participants at each time point noted; at Screening, the sample should be collected as soon as possible after the participant has completed the informed consent and PRO assessments
13. Informed consent for optional sub-studies (e.g. genetics research, PK) must be obtained before collecting a sample/performing procedure
14. Collected at Visit 2 or any time post-randomization if unable to collect at Visit 2
15. A spontaneous sputum sample will be collected at Screening/Day 1 (pre-dose) and Day 56 in participants who are willing and able to spontaneously produce sputum
16. PK Subgroup: Subset of participants (approximately 300) at selected sites – blood samples will be collected on site at Visit 3 (Day 14) and Visit 4 (Day 28) at trough (pre-dose), between 0-1 hour post-dose and between >1 hour to 6 hours post-dose (total of 3 samples at each visit).
17. Inhaler and Propeller Sensor training conducted by reviewing the Patient Information Leaflet and Propeller Sensor Instructions for Use Guide, respectively, with the participant. Additional training may be conducted at the discretion of the Investigator.
18. Day 1: Randomization and the first dose of double-blind study treatment administration (Visit 2/Day 1) should take place in the morning, as soon as possible following determination of eligibility and completion of the baseline PRO measures, including the EXACT-PRO questionnaire for the day of randomization, and FEV_1 measurement and no later than **24** hours after completing these assessments.
19. Daily recording via the clip-on Propeller Sensor for ELLIPTA and in the eCRF via review of the dose counter at Visits 3-6 (for countries where the Propeller Sensor for ELLIPTA is available) or in the eCRF only via review of the dose counter at Visits 3-6 (for countries where the Propeller Sensor for ELLIPTA is not available)
20. Daily recording via the clip-on Propeller Sensor for MDI and via the eDiary (for countries where the Propeller Sensor for MDI is available) or via the eDiary (for countries where the Propeller Sensor for MDI is not available or if nebulized albuterol [salbutamol] is used)

SoA: 12-Week Post-Treatment Follow-Up Period

Procedure	**Post-Treatment Follow-Up Period**			
Visit	7	8	9	Early Withdrawal
Day	Study Day 112 [10] (Day 28 of the Follow-Up Period	Study Day 140 [10] (Day 56 of the Follow-Up Period	Study Day 168 [10] (Day 84 of the Follow-Up Period	
Visit window	- 4/+3 days	- 4/+3 days	- 4/+3 days	
EFFICACY ASSESSMENTS				
Review eDiary	←==========→			
Collect eDiary			X	X
EXACT[1]	←==========→			
CAT[2]	X		X	X
SGRQ-C[3]	X		X	X
Clinic Visit FEV_1[4]	X	X	X	X
Rescue medication use[5]	X			
SAFETY ASSESSMENTS				
AE/SAE review	X	X	X	X
Concomitant medication review	X	X	X	X
COPD Exacerbation Assessment	X	X	X	X
Physical exam	X			X
Vital signs[6]	X			X[8]
12-lead ECG[6,7]	X			X[8]
Laboratory assessments (including hematology and biochemisty)[6]	X			X[8]
Urine pregnancy test (only WOCBP)	X[9]			X[8]

Procedure / **Visit**	**Post-Treatment Follow-Up Period**			
	7	8	9	Early Withdrawal
Day	Study Day 112 [10] (Day 28 of the Follow-Up Period	Study Day 140 [10] (Day 56 of the Follow-Up Period	Study Day 168 [10] (Day 84 of the Follow-Up Period	
Visit window	- 4/+3 days	- 4/+3 days	- 4/+3 days	
OTHER				
Review smoking status	X	X	X	X
Smoking cessation counselling	X	X	X	X
Health Care Resource Utilization (HCRU) Review	< ==========>			

CAT=COPD Assessment Test; EXACT=EXAcerbations of Chronic Pulmonary Disease Tool; FEV_1=forced expiratory volume in one second; IRT=Interactive Response Technology; WOCBP=women of child-bearing potential

1. Completed daily in the evening
2. Subjects should complete the CAT at the visits noted as well as 7 days post EXACT-defined day of recovery after exacerbation; the CAT will be completed prior to the SGRQ-C and other study assessments/procedures
3. Subjects should complete the SGRQ-C after completing the CAT and prior to other study assessments/procedures
4. Performed prior to dosing of concurrent COPD treatment(s) and pre-bronchodilator and post-bronchodilator (approximately 10 to 30 minutes following treatment with albuterol [salbutamol], administered as either four inhalations via the metered-dose inhaler [MDI] (i.e., 400 mcg) with valved-holding chamber or one nebulized treatment)
5. Daily recording via the clip-on Propeller Sensor for MDI and via the eDiary (for countries where the Propeller Sensor for MDI is available) or via the eDiary only (for countries where the Propeller Sensor for MDI is not available or if nebulized albuterol [salbutamol] is used)
6. Prior to dosing of concurrent COPD medication(s)
7. Single assessment
8. Procedure completed only if the Early Withdrawal Visit occurs prior to Day 112
9. If the urine pregnancy text result is positive, a blood sample for serum pregnancy testing will need to be conducted to confirm pregnancy status
10. Participants who discontinue from study treatment will move directly into the 12-Week Post Treatment Follow Up Period starting with Visit 7. Visits for these participants will not align to Day 112, 140, 168, rather will occur every 28 weeks following the study treatment discontinuation date.

- The timing and number of planned study assessments, including efficacy (including PRO), safety, PK, biomarkers, health economics or medical resource utilization, or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments, along with any changes to the randmisation including the possible addition of the 25mcg dose strength, must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

3.1. Study Rationale

Chronic obstructive pulmonary disease (COPD) refers to the two disease processes chronic bronchitis and emphysema. Inflammation in the lung has been linked to the pathogenesis of COPD. In COPD, tobacco smoke or other irritants activate epithelial cells and macrophages to release inflammatory mediators such as chemokines that attract neutrophils and T cells to the lung. The inflammation associated with COPD is characterized by a prominent infiltration of neutrophils in lung tissue and the airways. It is believed that the neutrophil, via elaboration of tissue destructive proteases and inflammatory mediators, plays a key role in the tissue destruction and decline in lung function that occurs in COPD.

Phosphoinositide 3-Kinase Delta (PI3Kd), a lipid kinase expressed predominately in leukocytes, is thought to hold much promise as a therapeutic target for inflammatory conditions such as chronic obstructive pulmonary disease (COPD) and asthma. PI3Kd is a member of the Class IA family of phosphoinositides 3-kinases (PI3Ks) that are involved in many cellular processes including cell growth, differentiation and migration. PI3Kd is thought to play a role in various epithelial responses relevant for the development of COPD. Therefore, a PI3Kd inhibitor may suppress a number of these processes [Kim, 2010]. Macrophages appear to be alternatively activated in COPD and their competence to phagocytose infective pathogens is reduced as a result of this alternative action. PI3Kd is one of the mediators involved in determining this alternative phenotype and therefore its inhibition could rebalance the macrophage activation towards a classic phagocytic phenotype [Weisser, 2011]. Macrophages would then be more competent in clearing bacterial infection, a major cause of exacerbations in COPD. The neutrophil and T cell are the two major inflammatory cells types of COPD and both are targeted by PI3Kd inhibitors. For example, a PI3Kd inhibitor prevents release of neutrophil elastase and reactive oxygen species (ROS) [Sadhu, 2003] and therefore could be useful in limiting tissue damage and prevent remodeling of the airways which leads to compromised lung function. In contract, PI3Kd should not globally inhibit neutrophil functions required for innate immune defense such as phagocytosis and bacterial killing.

PI3Kd inhibitors may also provide benefits in preventing infections by common airway bacterial pathogens such as S. pneumonia [Fallah, 2011]. In this report PI3Kd is shown to reduce the macrophage-derived cytokines required to mount an effective antibody response to S. pneumonia in the elderly. Furthermore, PI3Kd inhibition restores age-associated aberrant neutrophil migration [Sapey, 2014]. Activation of the PI3Kd pathway in critically ill patients has been linked to impairment neutrophil phagocytosis, which could be restored with a PI3Kd selective inhibitor [Morris, 2011]. Finally, PI3Kd activating mutations have recently been identified in groups of primary immunodeficient patients that suffer from viral infections and recurring lung bacterial infections due to mainly S. pneumonia and H. influenza. This results in progressive pulmonary sepsis and increasing morbidity and mortality [Angulo, 2013; Lucas, 2014].

Nemiralisib is a potent and highly selective inhaled PI3Kd inhibitor being developed as an anti-inflammatory for the treatment of inflammatory airways diseases. Therefore, it has the potential to be a novel therapy in patients with COPD.

This double-blind (Sponsor Open) study is primarily designed to assess the dose response, efficacy and safety of six dose regimens of nemiralisib (12.5, 50, 100, 250, 500, and 750 mcg QD) and placebo in addition to standard of care (SoC) for 12-weeks in participants with COPD who present with a moderate or severe acute exacerbation of COPD. The option to add a dose strength of 25 mcg following the results of an unblinded interim analysis has been included if further characterization of the lower end of the dose response curve is required.

Standard of Care (SOC) for the index exacerbation is defined for this protocol as treatment with oral/systemic corticosteroid(s) (prednisone 40 mg/day or equivalent) for 5 days **and** antibiotic[s] for 7 days; the dose and/or duration of prednisone (40 mg/day or equivalent) and/or the antibiotic can be modified according to the Investigator's/medically qualified designee's judgement or according to local country/institution practice. The start of SoC is defined as the start of either oral/systemic corticosteroids[s] or antibiotic[s] whichever is earliest. In addition, this study includes a 12-week Post-Treatment Follow-up Period to assess the potential benefit of nemiralisib following completion of treatment.

All study treatments will be administered once-daily in the morning (with the exception of Visit 2 where the dose may be administered up to 3:00pm, in cases where completion of the study assessments/procedures extends past noon) via the ELLIPTA inhaler with the clip-on Propeller Sensor (where available). In addition to double-blind study treatment and SoC treatment for the COPD exacerbation, other treatment(s) for the exacerbation (i.e., bronchodilators) and regular COPD maintenance therapy are permitted.

The information obtained from study 200879 will be used to select the optimally effective and safe dose of nemiralisib for further COPD studies. In addition, this study will evaluate and confirm the pharmacokinetic (PK) profile of nemiralisib.

3.2. Background

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation

that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [GOLD, 2017]. COPD is a major cause of disability, morbidity, and mortality, resulting in millions of deaths annually worldwide [GOLD, 2017] contributing significantly to health care costs [Darnell, 2013; Chapman, 2006]. In the United States, COPD is now the third leading cause of death [National Center for Health Statistics, 2016]. The morbidity and mortality associated with COPD are continuing to increase. Globally, it is estimated that about 3 million deaths were caused by COPD in 2015 (that is, 5% of all deaths globally in that year); and, by the year 2030, COPD is expected to be the third leading cause of death worldwide [WHO, 2016].

COPD is characterized by symptoms of chronic and progressive breathlessness (or dyspnea), cough, and sputum production which can be a major cause of disability and anxiety associated with the disease. Most COPD patients also suffer from periodic worsening of their COPD symptoms (COPD exacerbations). COPD exacerbations account for a significant proportion of COPD-related and total health care costs and are associated with an accelerated decline in lung function, health status, and increased risk for mortality with the cumulative risk for a next exacerbation or mortality increasing with each successive exacerbation [Donaldson, 2006; Suissa, 2012]. Despite several available therapies that have been shown to impact COPD exacerbations, many COPD patients continue to experience exacerbations of their disease, resulting in a large unmet medical need. Thus, therapies effective in further reducing COPD exacerbations and improving the respiratory symptoms associated with COPD will have a substantial impact on healthcare utilization and most importantly improvement in COPD patients' quality of life.

COPD refers to the two disease processes chronic bronchitis and emphysema, and inflammation in the lung has been linked to the pathogenesis of COPD. In COPD, tobacco smoke, other irritants, and/or bacterial colonization activate epithelial cells and macrophages to release inflammatory mediators such as chemokines that attract neutrophils and T cells to the lungs.

Exacerbations in COPD are driven by episodes of acute inflammation, usually following a viral or bacterial infection. The rate of moderate exacerbations (i.e., those treated with antibiotics and/or oral corticosteroids), as reported in a large observational clinical cohort study of patients diagnosed with COPD in the United States and the United Kingdom (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints, ECLIPSE) was 0.99 per patient year [Hurst, 2010]. The rate of severe exacerbations (i.e., those resulting in hospital admission) from the same observational study was 0.22 per patient year [Hurst, 2010]. Between a quarter (25% [McGhan, 2007]) and half (50% [Corral-Gudino, 2011]) of patients hospitalized for a COPD exacerbation will be re-hospitalized for another COPD exacerbation within the following 12 months.

While current maintenance therapies may reduce the rate of moderate to severe exacerbations in patients with COPD, some patients are particularly susceptible to repeated exacerbation events, resulting in frequent use of oral/systemic corticosteroids and/or antibiotics and, in some cases, recurrent hospital admissions. This patient phenotype is referred to as ‘frequent exacerbator’ [Hurst, 2010]. ‘Frequent exacerbators’ are now recognized as a major phenotype of COPD [Wedzicha, 2013; Miravitlles 2013].

The ECLIPSE clinical cohort study demonstrated that the prevalence of 'frequent exacerbators' varies by severity of COPD, from 22% in patients with Moderate COPD (GOLD Stage 2) to 47% in patients with Very Severe COPD (GOLD Stage 4) [Hurst, 2010].

Despite treatment, some patients do not regain their baseline lung function following a COPD exacerbation [Seemungal, 2000] and repeated events can lead to an accelerated decline in lung function, resulting in a worsening overall health related quality of life for patients and a significant burden on healthcare resources.

COPD patients with a viral infection have a significantly increased risk of developing a secondary bacterial infection [George, 2014]. Moreover, exacerbating patients with co-infections experience significantly increased lung impairment and longer hospitalizations [Papi, 2006]. There is an increased risk of a recurrent exacerbation during the first 8 weeks following an initial moderate to severe exacerbation [Hurst, 2009]. Thus, there is an unmet need for novel therapies that can treat moderate to severe COPD exacerbations more effectively by reducing the duration and severity, and can then also prevent the occurrence of respiratory bacterial infections. It is widely recognized that antibiotic resistance is a significant and growing global public health issue [Antibiotic Resistance. WHO Fact Sheet, 2016 (WHO, 2016), ; FDA: Combating Antibiotic Resistance, Consumer Health Information, 2011 (FDA, 2011); Public Health England ESPAUR Report, 2016 (ESPAUR, 2016)] and FDA and CHMP guidelines on development of drugs for treatment of bacterial infections [FDA, 2012; CPMP/EWP/558/95; 2011; EMA/CHMP/351889/2013, 2014] recognise the importance of the development of new anti-bacterials to human health; any medicine that has the potential to reduce the need for repeated courses of antibiotics will be an important addition to the treatment options in this setting.

PI3Kd is a lipid kinase expressed predominantly in leukocytes and thought to hold much promise as a therapeutic target for inflammatory respiratory conditions such as COPD and asthma [Barnes, 2003; Stark, 2015]. PI3Kd is a member of the Class IA family of phosphoinositides 3-kinases (PI3Ks) that are involved in many cellular processes, including cell growth, differentiation and migration. PI3Ks 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. PI3Kd has specific roles in mediating antigen receptor and cytokine signalling in T-cells, mast cells and B-cells [Okkenhaug, 2007] and roles in neutrophil chemotaxis and activation [Sadhu, 2003]. A PI3Kd inhibitor has the potential to inhibit major cell types responsible for the inflammation associated with both COPD and asthma.

In COPD, tobacco smoke or other irritants activate epithelial cells and macrophages to release inflammatory mediators such as chemokines that attract neutrophils and T cells to the lungs. PI3Kd is thought to play a role in a number of epithelial responses relevant for the development of COPD. Therefore, a PI3Kd inhibitor may be able to suppress a number of these processes [Kim, 2010]. A greater proportion of macrophages appear to be alternatively activated in COPD and their ability to phagocytose infective pathogens is reduced as a result of this alternative activation. PI3Kd is one of the mediators involved

in determining this alternative phenotype in macrophages and therefore it is proposed that inhibition of PI3Kd might rebalance macrophage activation towards a classic phagocytic phenotype [Weisser, 2011] facilitating clearance of bacteria, a major cause of exacerbation in COPD. The neutrophil and T cell are the two major inflammatory cell types involved in the pathogenesis of COPD and both are targeted by PI3Kd inhibitors.

Nemiralisib has demonstrated the ability to protect against and control bacterial infections in preclinical rodent models. This is coupled with recent observations that PI3Kd inhibition leads to a correction in vitro of aberrant neutrophil chemotaxis directionality in the blood of COPD patients. Furthermore, a human point mutation which results in a constitutively activated version of PI3Kd has recently been characterized where the majority of affected patients have recurrent lung infections with the same bacterial species which are seen in COPD patients and are known to drive exacerbations. Collectively these data suggests that repeat dosing with nemiralisib could potentially reduce the impact of an acute exacerbation, or prevent the onset of a secondary exacerbation.

Proinflammatory cytokines have been reduced by nemiralisib, both in preclinical rodent bacterial models, and COPD patient samples treated *in vitro*.

To date, nemiralisib has been administered to:

- Participants with COPD in three, Phase IIa studies:
    - Completed Studies:
        - PII115119: A double-blind (sponsor unblind), placebo controlled, randomised, parallel group study to evaluate the safety, tolerability and pharmacokinetics of multiple doses of GSK2269557 administered as a dry powder to COPD patients and assessment of dose response using sputum biomarkers.
        - PII116678: A randomised, double-blind (sponsor unblinded), placebo controlled, parallel-group, multicentre study to evaluate the efficacy and safety of GSK2269557 administered in addition to standard of care in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease
    - Ongoing Study
        - 201928: A randomised, double-blind, placebo-controlled study to evaluate the safety, efficacy and changes in induced sputum and blood biomarkers following daily repeat doses of inhaled GSK2269557 for 12 weeks in adult subjects diagnosed with an acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).
- Participants with asthma in a concluded (i.e., study conduct complete, reporting ongoing), Phase IIa study

  - 201543: A multi-centre, randomised, double-blind, placebo-controlled, crossover study to investigate the efficacy, safety, and tolerability of repeat doses of inhaled GSK2269557 in adults with persistent, uncontrolled asthma

- Participants with Activated Phosphoinositide 3-kinase Delta Syndrome (APDS), also referred to as p110delta-Activating mutation causing senescent T cells, Lymphadenopathy and Immunodeficiency (PASLI), in an ongoing, Phase IIa study (204745)

- Healthy volunteers – smokers and non-smokers

A detailed description of the chemistry, pharmacology, efficacy, and safety of nemiralisib is provided in the Nemiralisib (GSK2269557) Investigator's Brochure (IB)/IB Supplement(s).

3.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2269557 can be found in the corresponding Nemiralisib (GSK2269557) Investigator's Brochure (IB)/IB Supplement(s). The following section outlines the risk assessment and mitigation strategy for this protocol.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP): Nemiralisib		
Bronchospasm	Inhaled treatment	Participants will be allowed to continue regular COPD treatments and have SoC. More severe participants will have their treatment started in hospital.
Mucosal irritancy	Detected in 13-week toxicology study in the dog	Participants will be regularly monitored for AEs and a participant eDiary kept. Thus far, mucosal irritancy has not been observed in clinical studies.
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 review of reported terms, cough often occurred	To further evaluate this finding of post-inhalation cough immediately following dosing, during study Visits 2-6 in the 12-Week Double-Blind Treatment Period, Investigators (or medically qualified designees) will observe participants for post-inhalation cough within 5 minutes immediately following dosing. If coughing is observed, details will be recorded in the source documentation and in the eDiary/eCRF. In addition, outside of the clinic visits, participants will have the opportunity to report post-inhalation cough (as well as other changes in medical conditions/changes in medications) in the eDiary, which will be reviewed by the Investigator/medically qualified designee for reporting of any AEs/SAEs (See Section 9.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	The ICF will inform participants that in previous clinical trials, post-inhalation cough has been reported following nemiralisib administration via the DISKUS inhaler and that the post-inhalation cough is considered at least possibly causally related to nemiralisib. The ICF will instruct participants to promptly contact the investigative site if they experience post-inhalation cough, especially if the post-inhalation cough prevents them from correctly using the ELLIPTA inhaler, so that they can be further evaluated. An internal Safety Review Committee (iSRC) will have study oversight to ensure participant safety in study 200879 (See Appendix 3). Data (including data related to post-inhalation cough) will be reviewed by the iSRC on a periodic basis, as defined in the iSRC Charter, which is available upon request.
Nemiralisib may be a victim of cytochrome P450 3A4 (CYP3A4) drug interactions There is a risk that co-administration of nemiralisib with potent CYP3A4 inhibitors may increase systemic exposure to nemiralisib	Nemiralisib is an in vitro substrate of CYP3A4CyP3A4. Currently only limited in vivo information is available on the in vivo metabolism of nemiralisib in humans. In toxicology studies, no systemic toxicities were observed in any species following administration of nemiralisib via a variety of routes in studies of up to 3-month duration. These studies included	Co-administration with strong CYP3A4 inhibitors are not permitted. Acute administration (up to 14-day dosing) of some of the 3A4 inhibitors voriconazole, fluconazole, erythromycin and clarithromycin is, however, permitted. The extent of drug interaction between these inhibitors and midazolam (as a very worst case) can be interrogated using the Washington database [Hachad, 2010].

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	systemic exposure at no adverse effect levels > approximately 10-fold the systemic exposure following the maximum proposed clinical dose of 500 mcg. Considering the low sub milligram maximum dose selected of 750 mcg, any impact on metabolic inhibition by CYP3A4 inhibitors to increasing systemic exposure to above those tested in early studies (at/up to 6400 mcg) is considered minimal	Changes in systemic exposure to midazolam on co-administration with voriconazole, fluconazole, erythromycin and clarithromycin are predicted as < 10-fold, which is judged to be a safe acute threshold for nemiralisib, considering the lack of systemic toxicology in animal studies. Itraconazole, ketoconazole, and ritonavir are fully excluded since changes in systemic exposure are predicted as > 10-fold. Intravenous clarithromycin is permitted since the intravenous dose also reduces first pass exposure to the intestine and liver and it is only likely to be given for short durations. It is not necessary to exclude CYP3A4 enzyme inducers since any resulting decrease in systemic exposure (due to upregulation of CYP3A4) will reduce systemic exposure, thus reducing the risk of systemic toxicity.
Nemiralisib may be a perpetrator of CYP3A4 drug interactions due to the time dependent inhibition of 3A4 by nemaralisbib There is a risk that co-administration of nemiralisib with potent narrow therapeutic CYP3A4 substrates may increase systemic exposure of the 3A4 substrate	Nemiralisib is time-dependent inhibitor of CYP3A4. Although nemiralisib is a low dose inhaled drug, with predicted free Cmax at steady state < 1 nM, the influence of CYP3A4 time dependent inhibition is yet to be fully explored.	Sensitive CYP3A4 substrates with narrow therapeutic range; alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus are contraindicated. The use of theophylline however will be allowed, according to the approved label/Prescribing Information, via both intravenous and oral routes, since a mechanistic model constructed for nemiralisib,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		when co-administered with theophylline, suggests a negligible effect on theophylline exposure. Monitoring of participants receiving IV theophylline should be performed in line with normal practice.
Unknown risks to an embryo, fetus (unborn baby) or nursing infant	There are no studies with nemiralisib in pregnant women. Nemiralisib did not cause gene mutation or chromosomal damage in a bacterial mutagen assay, in vitro mouse lymphoma L5178Y cell assay and an in vivo mouse micronucleus test. Results suggest that nemiralisib does not present a genotoxic hazard to humans. No embryo-fetal development or fertility defects were observed in the female rat at doses up to 25 mg/kg/day following subcutaneous (SC) injection. Test article-related embryo-fetal toxicity was observed in the rabbit at the maximum dose of 11.2 mg/kg/day; the NOAEL for rabbit embryo-fetal development effects is 3.4 mg/kg/day SC.	As specified in the protocol: • Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate in this study • Female participants must be postmenopausal or using a highly effective method for avoidance of pregnancy while in this study • If a female participant becomes pregnant during the study, she should let the study doctor know immediately. The study treatment will be stopped and the participant will not be allowed to continue in the study • For women of child-bearing potential, a serum pregnancy test will be included in the laboratory panel collected at the Screening (Visit 1). For these participants, a urine pregnancy test will be performed during the 12-week Treatment Period at Visits 4 (Day 28), 5 (Day 56), 6 (Day 84) or Early Withdrawal Visit, and 7 (Day 112 of the study/Day 28 of the 12-week Follow-Up

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Period). If the urine pregnancy test result is positive, serum pregnancy testing will be conducted to confirm pregnancy status.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Shortness of breath, coughing, light headedness or fainting, and/or chest tightness during the spirometry measurements.		As specified in the informed consent form for this study, if any of these symptoms should occur, the participant will receive appropriate medical treatment.
Spirometry assessments performed during a moderate or severe COPD exacerbation.		If a participant is unable to achieve the required standard of spirometry per Section 9.1.1 during a moderate or severe COPD exacerbation, they will be permitted to continue in the study. The protocol has anticipated that this is likely for hospitalised participants and therefore spirometry will be repeated at discharge for a secondary endpoint.
Feeling faint, or experiencing mild pain, bruising, irritation or redness at the injection site during the blood withdrawals In rare cases, an infection where the needle entered the skin		The medically qualified site staff conducting the phlebotomy will follow standard medical practice to minimize these risks
Skin irritation from the ECG electrodes placed on the participant's chest		The medically qualified site staff conducting the ECG measurement will follow standard medical practice for performing the ECG
Risk of radiation from a chest X-ray		As specified in the protocol: • A chest X-ray (CT scan), for purposes of determining participant eligibility, will be performed only at the Screening (Visit 1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• A chest X-ray (conducted within 48 hours of diagnosis) for confirmation of a suspected case of pneumonia, is encouraged rather than required

3.3.2. Benefit Assessment

The outcomes of this study will provide information that may produce advances in knowledge of treatment of COPD, particularly the unmet need for more effective treatment of acute moderate and severe exacerbations of COPD, leading to a potential health benefit in the future for patients in this target population. The outcomes of this study will also help to determine the lowest effective and safe dose(s) of nemiralisib to be evaluated in future studies of nemiralisib.

3.3.3. Overall Benefit:Risk Conclusion

The benefit:risk for nemiralisib is supportive of further clinical evaluation in Phase IIb development. Study 200879 is designed to determine whether nemiralisib could have the potential as a new therapeutic option for the treatment of acute moderate and severe exacerbations of COPD. The data from this study will also provide information that may contribute to advances in the knowledge of acute exacerbations of COPD and may lead to a potential future health benefit in the clinical management of patients in this target population.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • To characterize the dose response of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Change from baseline in Clinic Visit trough forced expiratory volume in one second (FEV_1) at Day 84 measured post-bronchodilator • Baseline is defined as the post-bronchodilator FEV_1 measured prior to the first dose of double-blind study treatment on Day 1.
Secondary • To characterize the dose response and efficacy of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of moderate and severe exacerbations over the 12-Week Treatment Period • Time to next moderate/severe exacerbation following index exacerbation • Change from baseline in Clinic Visit trough FEV_1 measured pre and post-bronchodilator at Days 14, 28, 56, and 84 (Day 84: post-bronchodilator is the primary endpoint; pre-bronchodilator is a secondary endpoint) and at hospital discharge (only for participants who are hospitalized for the index

Objectives	Endpoints
	exacerbation) • Change from hospital discharge in clinic visit trough FEV_1 measured pre- and post-bronchodilator at Days, 14, 28, 56, and 84 (in participants hospitalized for index exacerbation only)
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptoms indicative of an exacerbation and on health status using Patient-Reported Outcomes (PROs) in participants diagnosed with an acute moderate or severe exacerbation of COPD	<u>EXAcerbations of Chronic Pulmonary Disease Tool (EXACT-PRO)</u> • Proportion of participants achieving the EXACT definition of recovery from the index exacerbation by Days 14, 28, 56, and 84 • Time to recovery from index exacerbation • Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT <u>COPD Assessment Test (CAT)</u> • Proportion of responders using the CAT at Treatment Days 28, 56, and 84, and following EXACT defined recovery from the index exacerbation • Change from baseline (Day 1) in CAT total score at Days 28, 56, and 84 and following EXACT defined recovery from the index exacerbation <u>St. George's Respiratory Questionnaire (SGRQ) Total Score</u> • Proportion of responders on the SGRQ total score as measured by the SGRQ for COPD Patients (SGRQ-C) at Days 28, 56, and 84 • Change from baseline (Day 1) in SGRQ total score at Days 28, 56, and 84
• To evaluate the usage of rescue medication in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rescue medication use (occasions/day), averaged over each week of treatment and over the 84-day treatment period • The percentage of rescue-free days (24-

Objectives	Endpoints
	hour periods) during each week of treatment and over the 84-day treatment period
• To evaluate the population pharmacokinetics of nemiralisib in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Plasma nemiralisib concentrations and derived PK parameters (e.g., area under the curve [AUC (0-24) and AUC(0-t)], maximum concentration [Cmax], time at maximum concentration [Tmax], Ctrough) as appropriate will be collected in a subset of randomized participants (approximately 300) at selected sites as follows: trough (pre-dose) for the study treatment and post-dose for the study treatment from 0-1 hour and >1 to 6 hours on Days 14 and 28 of the 12-Week Treatment Period
• To assess the safety and tolerability of nemiralisib and placebo in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Incidence of adverse events (AEs; including serious AEs and AE of Special Interest [AESI]) • Vital signs (pulse rate, systolic and diastolic blood pressure) (measured at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • 12-lead electrocardiogram (ECG) assessments (performed at clinic Visits 1 [Screening], 3 [Day 14], 6 [Day 84], and 7 [Day 112] or Early Withdrawal Visit) • Clinical laboratory tests (hematology and chemistry; performed at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • Incidence of COPD exacerbations
Exploratory – 12-Week Treatment Period • To further characterize the dose response, and efficacy, of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of mild exacerbations over the 12-Week Treatment Period • Rate of all exacerbations (mild, moderate and severe combined) over the 12-Week Treatment Period • Time to next exacerbation (mild, moderate

Objectives	Endpoints
	and severe combined)
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptom stability following an exacerbation using Patient-Reported Outcomes in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Stability of symptoms post recovery measured using E-RS:COPD (Evaluating Respiratory Symptoms in COPD) and subscales from Randomization (Visit 2) to Day 84 (Visit 6)
• To explore the PK/PD relationship for nemiralisib	• Relationship between drug exposure and Pharmacodynamic responses (e.g. efficacy, heart rate, clinical laboratory analytes and blood biomakers) in the PK subset of participants (approximately 300) at selected sites.
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on HCRU in participants who experience a severe exacerbation of COPD	• Measures of HCRU related to severe exacerbations (e.g., hospitalizations, length of hospital stay, re-hospitalization within 30 days, number of Emergency Room [ER] visits, etc.)
• To evaluate the compliance with study treatment	• Number of actuations of the double-blind study treatment as measured by the clip-on Propeller Sensor (for countries where the Propeller Sensor for ELLIPTA is available)
• To evaluate inflammatory markers in blood in relation to acute exacerbation of COPD	• Blood samples collected at Screening through Visit 7 (as part of the clinical laboratory blood samples) for analysis of blood eosinophil counts and inflammatory mediators • Blood samples for analysis of inflammatory biomarkers (including but not limited to: high sensitivity C-reactive protein [hs-CRP], chemokine interferon-γ inducible protein 10 kDa (CXCL10)], and procalcitonin) collected at Visit 1 (Screening)
• To evaluate inflammatory and infective markers in sputum in relation to acute	• Spontaneous sputum sample for analysis of

Objectives	Endpoints
exacerbation of COPD	inflammatory and infective markers collected at Screening/Day 1 (pre-dose) and Day 56 in participants who are willing and able to provide a sample
Exploratory – Follow-Up Period To evaluate the potential post-treatment impact of double-blind study treatment during the 12-Week Post-Treatment Follow-Up Period	• Change from baseline (Day 84) in Clinic Visit trough FEV_1 measured pre- and post-bronchodilator at Day 112, 140 and 168 • Rate of moderate and severe COPD exacerbation(s) during the 12-Week Follow-Up Period • Rate of moderate and severe COPD exacerbation(s) over the 24-week study duration • Time to next exacerbation following cessation of double blind study treatment • Proportion of responders using the CAT at Days 112 and 168 • Change from baseline (Day 1) in CAT Total score at Days 112 and 168) • Proportion of responders on the SGRQ Total Score as measured by the SGRQ-C at Days 112 and 168 • Change from baseline (Day 1) in SGRQ total score at Days 112 and 168 • Severity of subsequent HCRU exacerbation defined by EXACT • E-RS: COPD and subscales from last dose of double-blind study treatment • Rescue medication use up to Day 112

5. STUDY DESIGN

5.1. Overall Design

This is a Phase IIb, multicenter, randomized, stratified, double-blind (Sponsor Open), placebo-controlled, parallel-group study in participants who present with an acute moderate or severe exacerbation of COPD requiring SoC.

Standard of Care (SoC) for the index exacerbation is defined for this protocol as treatment with oral/systemic corticosteroid[s] (prednisone 40 mg/day or equivalent) for 5 days **and** antibiotic[s] for 7 days; the dose and/or duration of prednisone (40 mg/day or equivalent) and/or the antibiotic can be modified according to the Investigator's/medically qualified designee's judgement or according to local country/institution practice. The start of SoC is defined as the start of either oral/systemic corticosteroids[s] or antibiotic[s] whichever is earliest.

In addition to double-blind study treatment and SoC treatment for the COPD exacerbation, other treatment(s) for the exacerbation (i.e., bronchodilators) and regular COPD maintenance therapy are permitted.

Participants will be randomised in a ratio of 3:1:1:1:1:1:3 to receive placebo, or nemiralisib doses of 12.5 mcg, 50 mcg, 100 mcg, 250 mcg, 500 mcg or 750 mcg. The option to add a dose strength of 25 mcg following the results of an unblinded interim analysis has been included if further characterization of the lower end of the dose response curve is required.

Patients will be stratified according to their index exacerbation: moderate or severe, and whether or not they are in the PK substudy. The definition of moderate and severe exacerbations is given in Appendix 9:

This study consists of a Screening Period, a 12-Week Treatment Period and a 12-Week Post-Treatment Follow-Up Period. Participants will visit the hospital /clinic a minimum of eight to nine times over a 24-week period as shown in Figure 1. Randomization and the first dose of the double-blind study treatment administration (Visit 2/Day 1) should take place in the morning, as soon as possible following determination of eligibility and completion of the baseline PRO measures, including the EXACT-PRO questionnaire for the day of randomization, and FEV_1 measurement and no later than 48hrs after the start of SoC.

Note: In the event that completion of the assessments/procedures at Visit 2 (or in cases where Visit 1 and Visit 2 are conducted on the same day) extends past noon, the first dose of the double-blind study treatment administration may occur up until 3:00 pm on Day 1. After Day 1, dosing should take place in the morning each day through the end of the 12-Week Double-Blind Treatment Period

For participants who are hospitalized:

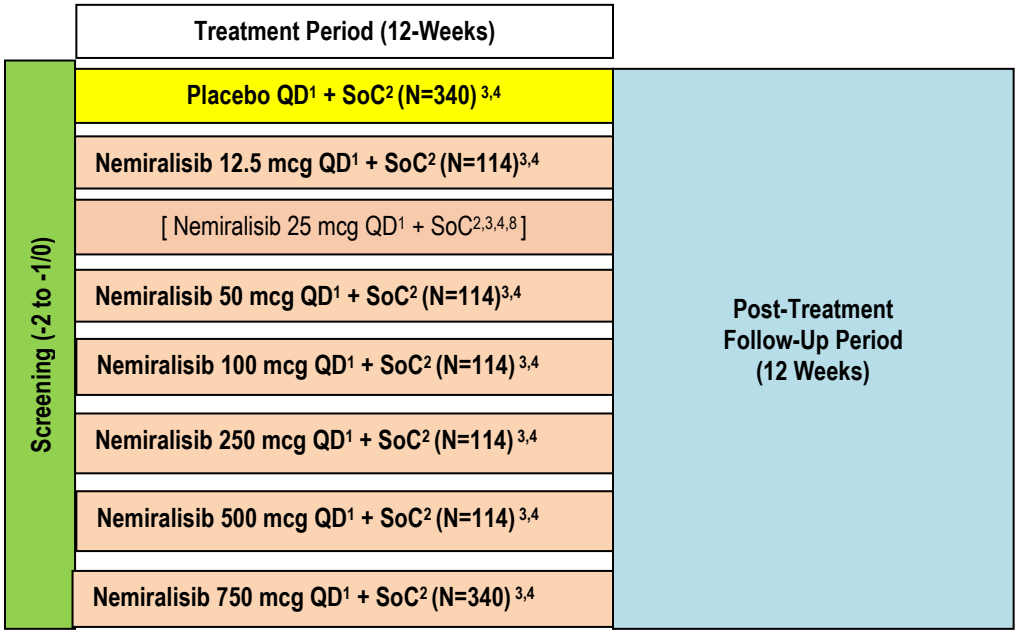
1. If discharge takes place before day 11, participants must then visit the unit/clinic on Day 14 (± 3 day) (Visit 3) for assessments.

2. If discharge takes place between Day 11 and Day 17 (inclusive), the assessments planned for Day 14 (Visit 3) may be completed on the day of discharge.

On the day of discharge, FEV_1 measurements should be performed in the morning prior to discharge, including pre-bronchodilator measurements and post-bronchodilator measurements.

The total duration of study participation is approximately 170 days.

Figure 1 Study Schematic



Clinic Visit:	1	2[5]	3	4	5	6[6]	7	8	9[7]
Day:	-2 to -1	1	14 (±3)	28 (±3)	56 (-4/+3)	84(-4/+3)	112 (-4/+3)	140 (-4/+3)	168 (-4/+3)

QD=once daily; SoC=Standard of Care

1. Inhalation Powder administered once-daily in the morning via the ELLIPTA inhaler
2. For this study, SoC for the index exacerbation is defined for this protocol as treatment of the COPD exacerbation with oral/systemic corticosteroid[s] (prednisone 40 mg/day or equivalent) for 5 days **and** antibiotic[s] for 7 days; the dose and/or duration of prednisone (or equivalent) and/or the antibiotic can be modified according to local country/institution practice. The start of SoC is defined as the start of either oral/systemic corticosteroids[s] or antibiotic[s] whichever is earliest
3. Note: subjects may receive additional treatment[s] for the exacerbation (e.g., bronchodilator) and will be on a background of regular COPD maintenance therapy
4. These figures are approximate and assume that no further adjustments to the randomization ratio are made. The actual sample sizes at the end of the study may be different, depending upon whether changes are made following the results of the unblinded interim analysis which may modify the planned allocation
5. Randomization and first dose of double-blind (Sponsor Open) study treatment
6. End of Treatment Period (last dose of double-blind [Sponsor Open] study treatment)
7. Last day of study
8. The option to add a dose strength of 25 mcg following the results of an unblinded interim analysis has been included if further characterization of the lower end of the dose response curve is required

PK Subgroup: Sparse PK sampling will be conducted at selected sites. The PK Subgroup will be identical to the main study in terms of the study population, design, and conduct, with the exception of blood draws (3 per visit on Days 14 and 28) for PK analysis.

An internal Safety Review Committee (iSRC) will have study oversight to ensure that it meets the highest standards of ethics and participant safety and to carry out the planned

interim safety data analyses/data reviews. Data will be reviewed by the iSRC on a periodic basis, as defined in the iSRC Charter. The iSRC, which will comprise a minimum of 3 people (including an independent statistician, and an independent clinician with experience in respiratory and general medicine), will be authorized to review unblinded interim safety analyses/data during the study; see Section 10.3.5.

5.2. Number of Participants

Approximately 1,667 participants will be screened (assumes an approximate 25% Screen Failure rate) to achieve approximately 1,250 randomized participants (assumes an approximate 20% withdrawal rate) such that approximately 1,000 participants complete the 12-week Treatment Period. Randomization will be stratified by index COPD exacerbation severity (moderate or severe) and by whether or not that participant is in the PK Subgroup, to ensure a balance across treatments within each strata.

The plan is to randomize approximately 340 participants each to the placebo and nemiralisib 750 mcg groups and approximately 570 participants across the other nemiralisib groups. The reason for inflating the sample size for a selected dose of nemiralisib (planned as the 750 mcg dose) and the placebo group is for the aim to increase precision around the pair-wise comparison between them for the key secondary objective of the reduction in the rate of re-exacerbations.

See Section 10.1 Sample Size Determination for additional details, including how screening failures and non-evaluable participants are defined.

5.3. Participant and Study Completion

A participant is considered to have completed the Treatment Period, if he/she has completed the last on-treatment study visit (Visit 6) and completed the study if he/she has completed all phases of the study including the last scheduled study visit (Visit 9).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA) for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomized, stratified, double-blind (Sponsor Open), parallel-group design. This is a well-established design to evaluate the dose response, efficacy and safety of an investigational drug in this phase of development. The 12-week Treatment Period duration detailed in this Protocol is considered adequate in order to evaluate efficacy (including lung function and PROs) in response to treatment intervention and to collect adequate safety measurements. The choice of a lung function endpoint (change from baseline in Clinic Visit trough FEV_1 at Day 84 measured post-bronchodilator) as the primary efficacy endpoint is a robust, well established, and objective means of demonstrating efficacy. The 12-Week Post-Treatment Follow-Up Period is considered adequate to evaluate efficacy and safety after study treatment has completed.

PK samples from a subset of randomized participants will also be collected in this study. Defining the optimum dose for later stages of development can be made more efficient by understanding the variability in the PK of a drug. In addition to the efficacy and safety endpoints, the study will evaluate the relationship between nemiralisib drug exposures and any other associated pharmacodynamic responses (e.g. efficacy, heart rate, clinical laboratory analytes and blood biomarkers).

This study will include a placebo arm to allow a comprehensive determination of the dose-response and to measure the absolute effect of nemiralisib. Inclusion of a placebo arm will also allow a more robust exploration of the therapeutic index of nemiralisib.

All participants in each of the nemiralisib treatment groups and in the placebo group will also receive SoC for their exacerbation of COPD and continue their regular COPD maintenance treatment throughout the study.

5.5. Dose Justification

Six doses of nemiralisib (12.5, 50, 100, 250, 500, and 750 mcg QD) and placebo will initially be evaluated in this study. An additional dose strength of 25 mcg may be added following the results of an unblinded interim analysis if further characterization of the lower end of the dose response curve is required. This study will, in an adaptive manner, aim to provide the data to select the minimal, optimally effective and safe dose of nemiralisib for use in further clinical studies of COPD.

The range of doses (12.5 mcg to 750 mcg QD) of nemiralisib in this study was selected based upon the results of the Proof-of-Concept (PoC) study PII116678 (similar population) in combination with additional clinical study PK and PK/PD information in patients and healthy volunteers. The PD endpoint used for dose prediction is based upon pharmacology, in particular the expected effect on the inhibition of the target PI3Kd enzyme due to the lack of precedence for this target mechanism as well as the patient population. Therefore, a dose predicted to achieve a certain level of target inhibition may not translate into the same level on downstream processes, in particular FEV_1, for example. Further information on these nemiralisib studies may be found in the Nemiralisib (GSK2269557) Investigator's Brochures (IB). The 12.5 mcg dose is expected to result in <50% target inhibition within the dosing window which for an inhibitor is not expected to translate to any patient outcome measure. However; since the precise dose response relationship is unknown within the patient population, target inhibition levels of <50% will be explored. The adaptive design of the study will allow the modification of the dose range based on efficacy. The nemiralisib 100 mcg, 250 mcg and 500 mcg doses are expected to achieve > 80% target inhibition and, therefore, could potentially define an efficacious dose level. The 750 mcg dose is included as a potential supra-therapeutic dose, to help establish the therapeutic index for nemiralisib and to assess whether or not an efficacy plateau has been achieved. Data from this trial will enable a better understanding of the relationship of the target engagement prediction with the downstream translation to other more clinically relevant (e.g., FEV_1) outcomes within this population.

By evaluating a range of doses from 12.5 mcg to 750 mcg of nemiralisib, it will be possible to assess the dose response of nemiralisib as measured by change from baseline in FEV_1. The data will provide information in determining the therapeutic index of nemiralisib and in selecting the minimal effective and safe dose to be carried forward in the Phase III COPD program.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

1. 40 to 80 years of age, inclusive, at Screening (Visit 1).

Type of Participant and Disease Characteristics

2. **Diagnosis:** An established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [GOLD, 2017] as follows:

   "*Chronic obstructive pulmonary disease is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.*"

3. **Smoking History:** Current or former cigarette smoker with a history of cigarette smoking of ≥10 pack-years. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening (Visit 1).

   Number of pack years = (number of cigarettes per day / 20) x number of years smoked) (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years both equal 10 pack-years)

4. **Current Acute Exacerbation of COPD:** Acute exacerbation of COPD requiring an escalation in therapy to include oral/systemic corticosteroid(s) (prednisone 40 mg/day or equivalent) for 5 days **and** antibiotic(s) for 7 days; the dose and/or duration of prednisone (40 mg/day or equivalent) and/or the antibiotic can be modified according to the Investigator's/medically qualified designee's judgement or according to local country/institution practice. Acute exacerbation to be confirmed by an experienced physician and to represent a recent worsening of at least two major and one minor symptoms, one major and two minor symptoms, or all 3 major symptoms.

   I. Major symptoms:

      i. Subjective increase in dyspnea

ii. Increase in sputum volume

iii. Change in sputum colour

II. Minor symptoms:

i. Increased cough

ii. Increased wheeze

iii. Sore throat

iv. Colds (nasal discharge and/or nasal congestion)

v. Fever (oral temperature >37.5 °C) without other cause

Weight

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

Sex

6. **Male** and female subjects are eligible to participate in the study.

a. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

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

OR

ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the 12-Week Double-Blind Treatment Period and for at least 5 half-lives (10 days) after the last of double-blind study treatment.

Informed Consent

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

6.2. Exclusion Criteria

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

Medical Conditions

1. **Asthma:** Current diagnosis of asthma, according to the Global Initiative for Asthma [GINA, 2017]. Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD.

2. **Acute respiratory acidosis/invasive mechanical ventilation**: pH < 7.30 or the need for invasive mechanical ventilation.

3. **Moderate/severe exacerbation of COPD for which SoC was started >48 hours since diagnosis**.

4. **Chest X-ray (or CT scan):** A chest X-ray (or CT scan) that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray (or CT scan) must be taken at Screening (Visit 1). **For sites in Germany:** if a chest X-ray (or CT scan) within 1 year of Screening (Visit 1) is not available, approval to conduct a diagnostic chest X-ray (CT scan) will need to be obtained from the Federal Office for Radiation Protection (BfS).

5. **Pneumonia:** Clinically significant pneumonia, identified by chest X-ray (CT scan) at Screening.

6. **Other respiratory disorders:** A diagnosis of α1-antitrypsin deficiency as the underlying cause of COPD, active tuberculosis, lung cancer, clinically overt bronchiectasis (Note: focal bronchiectasis is not exclusionary), sarcoidosis, pulmonary fibrosis (*Note: focal fibrotic pulmonary lesions are not exclusionary*), primary pulmonary hypertension, interstitial lung diseases, or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the subject or affect the interpretation of the results.

7. **Other diseases/abnormalities:** A history or current evidence of clinically significant and unstable disease such as cardiovascular (e.g., patients requiring implanted cardioverter defibrillator [ICD], pacemaker requiring a rate set >60bpm, uncontrolled hypertension, New Your Heart Association Class IV [NYHA, 1994], known left ventricular ejection fraction <30%), neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), peptic ulcer disease, or hematological abnormalities. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk hrough participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study. (Note: Participants with adequately treated and well controlled concurrent medical conditions (e.g. hypertension or noninsulin-dependent diabetes mellitus [NIDDM]) are permitted to be entered into the study).

8. **Lung resection:** Having undergone lung volume reduction surgery or lung resection for any other reason e.g. lung carcinoma

9. **Liver disease:**
    - ALT > 2xULN
    - Total Bilirubin > 1.5xULN
        i. Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%
    - Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
    - Presence of hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to first dose of study treatment
    - Positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment
    - Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained
    - NOTE: due to time taken to conduct Hepatitis B and C analysis, participants may be randomised to the study before receiving these results. If a participant has a positive test result, they will need be withdrawn promptly from the study.
10. **Positive hepatitis C RNA** test result at Screening or within 3 months prior to first dose of study treatment. NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
11. **Cancer:** Carcinoma that has not been in complete remission for at least 5 years. Carcinoma *in situ* of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin are not excluded if the participant has been considered cured within 5 years since diagnosis.
12. **Contraindications:** History of allergy or hypersensitivity to any of the study medications (e.g. beta-agonists, PI3Kd inhibitors) or excipients of the inhalation powder (e.g., lactose). In addition, participants with a history of severe milk protein allergy that, in the opinion of the investigator, contraindicates the participant's participation are excluded.

Prior/Concomitant Therapy

13. **Cytochrome P450 3A4:**
    - **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 posaconazole is used as the 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, sirolimus and tacrolimus.
  - 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.

14. **Oxygen therapy:** Chronic treatment with long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for >15 hours a day. Oxygen prn use (i.e., ≤15 hours per day) is not exclusionary. Oxygen use during an exacerbation is permitted.

15. **Immunosuppressive therapy:** Chronic treatment with anti-Tumour Necrosis Factor (anti-TNF), anti-Interleukin-1 (anti-IL1), or any other immunosuppressive therapy within 60 days prior to the first dose of double-blind study treatment.

Prior/Concurrent Clinical Study Experience

16. **Other investigational treatment:** Any other investigational treatment within the following time periods prior to the first dose of double-blind study treatment in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product, whichever is longer.

    Note: Participants who participated in a previously completed study and/or were withdrawn from an ongoing study that included/includes nemiralisib are excluded from participating in this study.

17. **Multiple other investigational treatment:** Exposure to more than 4 investigational medicinal products within 12 months prior to the first dose of double-blind study treatment in the current study.

Diagnostic assessments

18. **Abnormal Clinically Significant Laboratory Finding:** A clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the exclusion criteria, outside of the reference range for the population being studied may be included if the Investigator (in consultation with the GSK Medical Monitor if required) documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

19. **Abnormal Clinically Significant 12-Lead ECG:** abnormal, clinically significant ECG finding (e.g. myocardial Infarction or demonstrating a clinically significant arrhythmia requiring treatment) at Screening (Visit 1) or upon repeat prior to randomization.

20. **QTcF:** QTcF >480 msec for participants with or without Bundle Branch Block, based on averaged QTcF values of triplicate ECGs.

21. **HIV antibody:** A positive test for HIV antibody at Screening.

    NOTE: due to time taken to conduct HIV antibody analysis, participants may be randomised to the study before receiving these results. If a participant has a positive test result, they will need be withdrawn promptly from the study

Other Exclusions

22. **Drug/alcohol abuse:** Known or suspected history of alcohol or drug abuse within the last 2 years.

23. **History of regular alcohol consumption:** Defined as an average weekly intake of >28 units for males or >21 units for females within 6 months of Screening (Visit 1). 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.

24. **Potential of non-compliance:** Participants at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.

25. **Questionable validity of consent:** Participants with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.
26. **Affiliation with investigator site:** Study investigators, sub-investigators, study coordinators, employees of a participating investigator or immediate family members of the aforementioned are excluded from participating in this study.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Participants will refrain from consumption of grapefruit or grapefruit juice, from the first dose of double-blind study treatment until the last dose of double-blind study treatment during the 12-week Treatment Period.

6.3.2. Caffeine, Alcohol, and Tobacco

Participants will:

- refrain from consuming drinks with high levels of caffeine such as tea, coffee, and cola drinks, on the morning of study hospital/clinic visits and prior to and during the spirometry and 12-lead ECG assessment (and for 6 hours prior the start of dosing until after collection of the PK sample[s] during a given visit for participants in the PK subgroup).

- abstain from consuming alcohol for 12 hours prior to and during the day when they visit the hospital/clinic and until their discharge/completion of the study visit on that day

- refrain from smoking (including cigarettes [including electronic cigarettes/pipes, vaporizers, cigars, pipes) for at least 1 hour prior to and during the spirometry and 12-lead ECG assessments (and until after collection of the PK sample[s] during a given visit for participants in the PK subgroup) conducted during the study hospital/clinic visits.

6.3.3. Activity

- Participants will abstain from strenuous exercise for ≥2 hours prior to spirometry and ECG assessments and before each blood collection for clinical laboratory tests/PK/biomarkers. Participants may participate in light recreational activities during the study visits (e.g., watching television, reading).

6.3.4. Medication Use Prior to/During Study Visits

Participants will:

- withhold the morning dose of usual scheduled COPD medications (permitted and/or blinded study treatment) on the morning of and prior to the start and

during the spirometry assessments, with the exception of albuterol [salbutamol] for post-bronchodilator spirometry assessment and if the usual COPD medication is required for treatment of an acute exacerbation of COPD

- withhold the use of supplemental/rescue bronchodilator (e.g., albuterol [salbutamol]) for ≥4 hours prior to pre-bronchodilator spirometry assessments, unless required for treatment of an acute exacerbation of COPD

If participants are unable to withhold their usual scheduled COPD medications and/or bronchodilator, or the investigator determines participant safety would be at risk, then these can be administered and the visit should proceed. However, spirometry should be delayed until at least 4 hours have elapsed since bronchodilator use, if possible, and if the spirometry testing remains within the appropriate time frame.

6.3.5. Environmental Exposure

Participants will avoid exposure to cold air for 15 minutes prior to and during spirometry assessments.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any serious adverse events (SAEs), and protocol deviation(s) (if they occurred during the screening process).

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once for the following reasons:

- Meeting Exclusion Criterion 3 -Moderate/severe exacerbation of COPD for which SoC was started >48 hours since diagnosis. The re-screening visit must be conducted at least 6 weeks following the resolution date of that exacerbation and at least 6 weeks following the last dose of oral/systemic corticosteroids and after the participant has been diagnosed with a subsequent, acute moderate or severe exacerbation of COPD requiring SoC
- Meeting Exclusion Criterion 5 - Clinically significant pneumonia, identified by chest X-ray [CT scan] at Screening. The re-screening visit must be conducted at least 6 weeks following the resolution date of the pneumonia, at least 6 weeks following the last dose of oral/systemic corticosteroid(s) and/or antibiotic(s) used to treat the pneumonia, and after the participant has been diagnosed with a subsequent, acute moderate or severe exacerbation of COPD requiring SoC
- In rare instances, participants failing for other reasons may be eligible for re-screening.

Re-screening of participants must be approved by the central GSK team prior to re-screening. Only one re-screening is allowed per participant. Re-screened participants

must be assigned a new participant number and will be entered into the eCRF again. Re-screened participants must provide informed consent again and must meet all of the protocol-specified Inclusion Criteria and none of the Exclusion criteria and must repeat all of the Screening Visit procedures at the Re-Screen Visit to be eligible to continue to randomization.

7. TREATMENTS

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

7.1. Treatments Administered

GSK Clinical Trials Supplies will provide the investigational products for use in this study. All blinded study treatments will be delivered via the ELLIPTA. The ELLIPTA will include the clip-on Propeller Sensor for ELLIPTA for countries where the Propeller Sensor for ELLIPTA is available. The ELLIPTA provides a total of 30 doses.

Participants will be assigned to treatments in accordance with the randomisation schedule generated by Clinical Statistics, using validated internal software. The randomization will be stratified by severity of the index exacerbation, moderate or severe (per definitions in Section 5.1 and Section 12.9), and by whether or not the participant is in the PK Subgroup.

Following Screening, eligible participants will be randomized (3:1:1:1:1:1:3) to receive placebo or one of the following six treatments, administered as one inhalation each morning for 12 weeks:

- Placebo
- nemiralisib 12.5 mcg
- [nemiralisib 25 mcg]*
- nemiralisib 50 mcg
- nemiralisib 100 mcg
- nemiralisib 250 mcg
- nemiralisib 500 mcg
- nemiralisib 750 mcg

* The additional dose strength of nemiralisib 25 mcg may be added following the results of an unblinded interim analysis if further characterization of the lower end of the dose response curve is required.

In accordance with the adaptive design of this protocol, randomisation ratios may change following results of an unblinded interim analysis.

Double-blind study treatment will be started as soon as possible after screening and baseline assessments (e.g., EXACT, CAT, SGRQ, FEV_1) are completed and should be within 48 hrs of the start of SoC.

Note: In the event that completion of the assessments/procedures at Visit 2 (or in cases where Visit 1 and Visit 2 are conducted on the same day) extends past noon, the first dose of the double-blind study treatment administration may occur up until 3:00 pm on Day 1. After Day 1, dosing should take place in the morning each day through the end of the 12-Week Double-Blind Treatment Period.

In addition, all participants will receive rescue medication e.g., supplemental albuterol [salbutamol] MDI or nebules to be used on an as-needed basis throughout the study up through Visit 7. MDI will include the clip-on Propeller Sensor for MDI for countries where the Propeller Sensor for MDI is available. For all sites, this medication will be sourced locally where possible. After Visit 7, Investigators will prescribe appropriate rescue medication.

A web-based Interactive Response Technology (IRT) will be used to assign participants to treatment.

Descriptions of the investigational study treatments are provided in Table 1.

Table 1 Descriptions of the Investigational Study Treatments

Study Treatment Name:	Nemiralisib ELLIPTA	Placebo ELLIPTA
Dosage formulation:	Nemiralisib succinate blended with lactose and magnesium stearate[1]	lactose
Unit dose strength(s)/Dosage level(s):	Dry Powder Inhaler (single-strip presentation unless otherwise noted) with 30 doses per inhaler 12.5 mcg or [25 mcg][2] 50 mcg or 100 mcg or 250 mcg or 500 mcg or 750 mcg (dual-strip ELLIPTA with 250 mcg/blister in one strip and 500 mcg/blister in the second strip)	Dry Powder Inhaler (single-strip presentation) with 30 doses per inhaler
Route of Administration	Oral inhalation	Oral inhalation
Dosing instructions:	Inhale ONCE in the MORNING as directed [3]	Inhale ONCE in the MORNING as directed [3]
Packaging and Labeling	Study Treatment will be provided in a foil overwrap. Each foil overwrap will be labeled as required per country requirement.	Study Treatment will be provided in a foil overwrap. Each foil overwrap will be labeled as required per country requirement.
Manufacturer	GlaxoSmithKline	GlaxoSmithKline

1. Magnesium stearate 0.4% w/w of total drug product
2. The option to add a dose strength of 25 mcg following the results of an unblinded interim analysis has been included if further characterization of the lower end of the dose response curve is required
3. The first dose taken at randomisation may be in the early afternoon, up to 3:00pm to allow for all screening and randomisation assessments to be performed.

7.1.1. Medical Devices

- There are no GSK-manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study.
- Other medical devices (not manufactured by or for GSK) provided for use in this study are the valved-holding chamber and the clip-on Propeller Sensor.
- Instructions for medical device use are provided in the corresponding manufacturer's instructions for use.
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 9.2).

7.2. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule as discussed in this section; however, the maximum daily dose of nemiralisib is not planned to exceed 750 mcg and the total number of participants to be randomized is not planned to exceed approximately 1,250.

Depending upon the findings of the iSRC reviews (See Appendix 3), randomization to a given study treatment arm(s) may be halted and the randomization allocation for the given study treatment arm(s) may be re-allocated to another study treatment arm(s).

Depending upon the findings of interim analyses adjustments to the randomization ratio across the nemiralisib doses may be made to help optimize the characterization of the dose response profile.

The additional dose strength of nemiralisib 25 mcg may be added following the results of an unblinded interim analysis if further characterization of the lower end of the dose response curve is required.

7.3. Method of Treatment Assignment

All participants will be centrally randomized using an Interactive Response Technology (IRT). Before the study is initiated, the log-in information and directions for the IRT will be provided to each site.

A centrally randomised schedule will be utilized to randomize participants into one of the seven treatment arms. Participants will be stratified by severity of the index exacerbation (moderate or severe) and whether or not the participant will provide PK samples. If required, additional schedules will be created for each change to the randomization ratios.

Study treatment will be dispensed at the study visits summarized in the SoA.

Returned study treatment should not be dispensed to the participants.

7.4. Blinding

The IRT will be programmed with blind-breaking instructions.

The 12-Week Treatment Period will be a double-blind (Sponsor Open) study and the following will apply.

- The investigator or treating physician may unblind a participant's treatment assignment only in the case of an emergency OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.

  Note: ***GSK must be notified of the decision to unblind.*** *If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding. The date and reason for the unblinding must be fully documented in the eCRF. A participant will be withdrawn from study treatment if the participant's treatment code is unblinded by the investigator*

Specific members of the statistics and programming teams will have access to the unblinded randomization schedules, where participants are only unblinded once randomization has taken place and purely for the purposes of unblinded efficacy interim analyses. Specific members of the study team (defined in the RAP and Study Results Dissemination Plan [SRDP]) will be presented unblinded summary level data at interim analysis time points (See Section 10.3.5).

Members of the iSRC will have access to the unblinded randomization schedules, where participants are only unblinded once randomization has taken place and purely for the purposes of unblinded safety review. Members of the iSRC will be provided unblinded summary level data at interim analysis time points (See Section 10.3.5). Members of the iSRC and method of receipt of data will be documented in the iSRC charter.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. 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).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.
5. 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.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

7.6.1. 12-Week Double-Blind Treatment Period

- During study Visit 2 (Randomization Visit/Day 1) through Visit 6 (Day 84) during the 12-week Treatment Period, when participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be documented in the eCRF for all participants. For countries where the clip-on Propeller Sensor for ELLIPTA is available, date and time of each dose administered in the clinic will also be captured via the Sensor.
- Between study visits during the 12-week Treatment Period, when participants self-administer study treatment at home, compliance with double-blind study treatment will be assessed by the study site staff by reviewing the dose counter on the ELLIPTA during the inhaler dispensing and return visits and by recording the compliance in the eCRF. For countries where the clip-on Propeller Sensor for ELLIPTA is available, compliance will also be captured via the Sensor.
- A record of the number of ELLIPTA inhalers dispensed to and taken by each participant 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 eCRF.

Participant compliance with double-blind study treatment will be assessed at Visits 3 through 6, by reviewing the clip-on Propeller Sensor for ELLIPTA data (for countries where the Propeller Sensor for ELLIPTA is available) or by reviewing the dose counter on the ELLIPTA (countries where the Propeller Sensor for ELLIPTA is not available). Participants must be ≥80% to ≤120% compliant in taking study treatment between-on-treatment visits. Participants who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the participant's source document. If the double-blind study treatment is prematurely discontinued during the 12-Week Double-Blind Treatment Period or study treatment

compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss participant eligibility for continued participation in the study.

7.6.2. 12-Week Post-Treatment Follow-up Period

During the 12-week Post-Treatment Follow-up Period, there will not be any formal assessment of compliance. However, all concomitant medications (COPD and non-COPD) will be captured in the source documents and eCRF.

7.7. Concomitant Therapy

For participants who are randomized, any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment (Screening Visit) or receives during the study (including the 12-week Double-Blind Treatment Period and the 12-week Post-Treatment Follow-up Period) must be recorded in the source documents and eCRF along with:

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

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

In addition, all COPD medications taken within 3 months prior to Visit 1 (Screening) should be recorded in the participant's source and in the eCRF.

7.7.1. Permitted Medications and Non-Drug Therapies

7.7.1.1. COPD Medications and Non-Drug Therapies

- To be eligible for this protocol, at Screening, participants must present with a moderate or severe acute exacerbation of COPD requiring treatment with SoC. Standard of Care (SoC) for the index exacerbation is defined for this protocol as treatment with oral/systemic corticosteroid[s] (40 mg/day prednisone or equivalent) for 5 days and antibiotic[s] for 7 days, to be confirmed by an experienced physician (See Inclusion Criterion 4); the dose and/or duration of prednisone (40 mg/day or equivalent) and/or the antibiotic can be modified according to the Investigator's/medically qualified designee's judgement or according to local country/institution practice. The start of SoC is defined as the start of either oral/systemic corticosteroids[s] or antibiotic[s] whichever is earliest. SoC must be documented in the participant's source documentation and in the eCRF. The use of other medications for treatment of the index COPD exacerbation and any subsequent COPD exacerbation(s), if applicable, is at the discretion of the Investigator or medically qualified health care personnel. Use

of medication for treatment of subsequent exacerbations does not need to follow the SoC requirements for the Index exacerbation.

- In addition, participants are allowed to continue their regular COPD treatments (e.g., long-acting bronchodilators, long-acting beta2-agonist/corticosteroid combinations, long-acting muscarinic antagonist/long-acting bronchodilator combinations, etc.) for the duration of the study (including the 12-Week Double-Blind Treatment Period and during the 12-Week Post-Treatment Follow-Up Period). However, participants must withhold the morning dose of usual scheduled COPD medications (permitted and/or double-blind study treatment) on the morning of and prior to the start and during the spirometry assessments, with the exception of albuterol [salbutamol] for post-bronchodilator spirometry assessment and if the usual scheduled COPD medication is needed for treatment of an acute exacerbation of COPD, where possible.
    - ***Note:*** *Modification(s) of the dosing regimen for the regular COPD treatments is(are) permitted as deemed medically appropriate by the Investigator/medically qualified designee; the modifications will be recorded in source documents and eCRF*
- Other concomitant COPD medications may be allowed at the discretion of the Investigator following consultation with the GSK Clinical Investigation Leader/Medical Monitor, with the exception of short-acting anticholinergics for use as rescue medication (See Section 7.7.2.1).
- Oxygen for intermittent use or PRN therapy ≤15 hours per day is allowed. LTOT or nocturnal oxygen therapy required for >15 hours is excluded throughout the study.

The study site will supply each randomized participant with albuterol [salbutamol] MDI for use in performing the post-bronchodilator FEV_1 assessments and as rescue medication for use as needed throughout the 12-Week Treatment Period for treatment of acute symptoms of COPD. Albuterol [salbutamol] will be provided locally by GSK. In addition, participants may use albuterol [salbutamol] nebules if they have a nebulizer.

Although the use of rescue albuterol [salbutamol] medications is allowable at any time during the study, its use should be delayed for at least 4 hours prior to completing the pre-bronchodilator spirometry assessments, unless required for treatment of an acute exacerbation of COPD. The participants' use of the study-supplied albuterol [salbutamol] will be captured via the clip-on Propeller Sensor for MDI (for countries where the Propeller Sensor for MDI is available) or via the eDiary (for countries where the Propeller Sensor for MDI is not available or for participants who are supplied nebulized albuterol [salbutamol]).

For assessment of change from baseline in Clinic Visit FEV_1 post-bronchodilator, the bronchodilator will be standardized as albuterol [salbutamol], administered as either four inhalations via the MDI (i.e., 400 mcg) with valved-holding chamber or one nebulized treatment. It is anticipated that participants who are enrolled into the study will receive albuterol as part of the routine treatment of AECOPD during visit 2. In this instance

spirometry should be scheduled to coincide with this treatment to allow post-bronchodilator recordings to be measured.

7.7.1.2. Non-COPD Medications and Non-Drug Therapies

All medications for other disorders are permitted as long as the dose remains constant wherever possible and their use would not be expected to affect the efficacy (especially lung function) or safety assessments.

The use of a continuous positive airway pressure (CPAP) device or non-invasive positive pressure ventilation (NIPPV) is permitted during the study, provided that this therapy was initiated prior to Screening and the participant is on a stable regimen. If CPAP or NIPPV therapy is initiated during the 12-Week Double-Blind Treatment Period, the participant will need to be withdrawn from double-blind study treatment but can continue in the study for collection of data. Patients that require acute use of CPAP or NIPPV may not be enrolled. Use of this therapy is to be recorded in the source document and eCRF.

Participation in the acute or maintenance phase of a Pulmonary Rehabilitation Program during the study (double-blind Treatment Period and/or Post-Treatment Follow-up Period) is permitted. Participation is to be recorded in the source document and eCRF.

7.7.2. Prohibited Medications and Non-Drug Therapies

7.7.2.1. COPD Medications and Non-Drug Therapies

Short-acting anticholinergics (e.g., ipratropium bromide) for use as a rescue medication are excluded from the Screening Visit through completion of Visit 7, unless required for treatment of an acute exacerbation of COPD if albuterol [salbutamol] is not prescribed or readily available. If medically appropriate, the use of the rescue anticholinergic up through Visit 7 may be replaced with the study-provided albuterol [salbutamol] MDI at the discretion of the Investigator/medically qualified designee.

7.7.2.2. Non-COPD Medications and Non-Drug Therapies

Concomitant use of strong inhibitors of cytochrome P450 3A4 and concomitant use of sensitive narrow therapeutic index CYP3A4 substrates is not permitted. See Section 6.2 Exclusion Criteria 13 for detail.

7.8. Treatment after the End of the Study

GSK will not provide treatment after the end of the 12-week double-blind treatment period. The Investigator is responsible for ensuring that consideration has been given to the care of the participant's medical condition on completion of 12-week double-blind treatment period.

Participants will be prescribed appropriate COPD therapy at the completion of Visit 6 or at the Early Withdrawal Visit, which may or may not be the usual COPD daily medication that form their maintenance therapy during the 12-week treatment period.

8. DISCONTINUATION CRITERIA

A participant may voluntarily discontinue participation in this study at any time (including during the Screening Period, the 12-Week Double-Blind Treatment Period or during the 12-Week Post-Treatment Follow-Up Period). The Investigator may also at his/her discretion discontinue a participant from this study at any time. Every effort should be made by the Investigator to keep the subject in the study.

Participants who are withdrawn from the study will not be replaced and cannot be re-screened.

The primary reason for subject withdrawal will be recorded in the eCRF (see Section 8.2).

8.1. Discontinuation of Study Treatment

A participant may be discontinued from study treatment but continue in the study for collection of data (including efficacy and safety data) and to minimize missing data. Participants who discontinue from study treatment will move directly into the 12-Week Post Treatment Follow Up Period starting with Visit 7, 28 days following the discontinuation date.

If a higher than expected number of participants prematurely discontinues double-blind study treatment or prematurely discontinues from the study, additional participants may be randomized, at the discretion of the Sponsor.

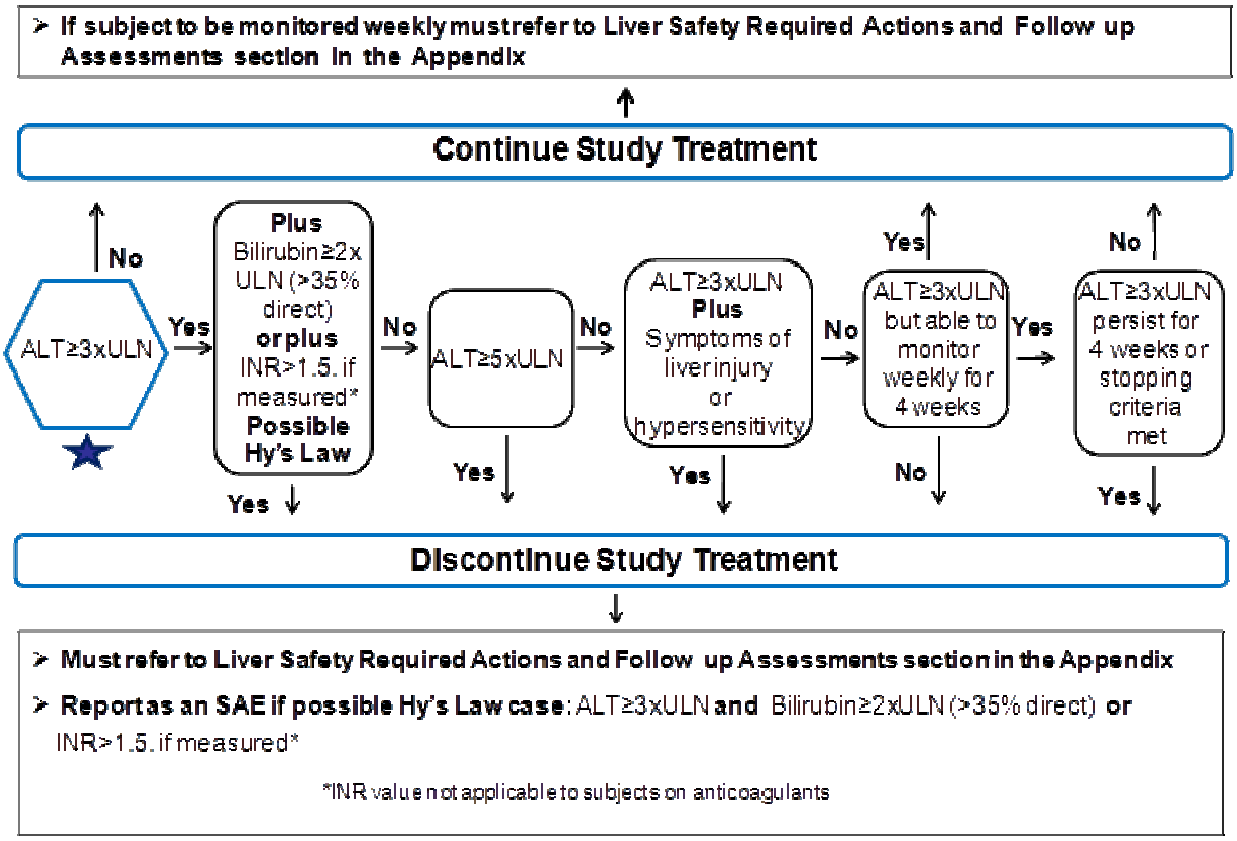
8.1.1. Liver Chemistry Stopping and Follow-up Criteria

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

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

- a participant meets one of the conditions outlined in the algorithm below
- in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

Figure 2 Liver Chemistry Stopping and Increased Monitoring Algorithm



Refer to Appendix 7 for required Liver Safety Actions and Follow-Up Assessments.

8.1.2. QTc Stopping Criteria

In this study, GSK is contracting with an external vendor to provide standardized 12-lead ECG equipment and centralized ECG overreads for all participating sites (Section 9.4.3).

The same QT correction formula (Fridericia's) *must* be used throughout the study for all participants. Safety ECGs and other non-protocol specified ECGs are an exception.

The QTc criteria should be based on the averaged QTc value of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period.

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc >530 msec (with or without underlying Bundle Branch Block) OR Uncorrected QT >600 msec
- Change from baseline of QTc > 60 msec

In addition, participants should be excluded (Screening) or be discontinued from study treatment if they have an abnormal, clinically significant ECG finding as defined in the ECG manual.

8.1.3. Pneumonia

Presumptive diagnosis or radiographically confirmed (See definition in "COPD Exacerbation" Section 9.1.2) requires discontinuation of study treatment.

If a subject is withdrawn due to pneumonia, the AE/SAE section and the pneumonia/ chest X-ray section, if applicable, of the eCRF should be completed and the subject should be followed until clinical resolution of the pneumonia.

8.1.4. Acute respiratory acidosis/invasive mechanical ventilation

A pH < 7.30 or the need for invasive mechanical ventilation requires discontinuation of study treatment.

8.1.5. Other Safety Stopping Criteria

For a study participant, other safety stopping criteria include, but are not limited to:

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

8.1.6. Pregnancy

A female participant must be discontinued form study treatment if a positive serum pregnancy test is obtained.

8.1.7. Temporary Discontinuation

A participant may be withdrawn from study treatment as discussed in Section 8.1 but continue in the follow-up period of the study for collection of efficacy and safety data.

8.1.8. Rechallenge

8.1.8.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time during the study (including the Screening Period, the 12-Week Double-Blind Treatment Period or the 12-Week Post-Treatment Follow-Up Period) at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.

If a higher than expected number of participants prematurely discontinues double-blind study treatment or prematurely discontinues from the study, additional participants may be randomized, at the discretion of the Sponsor.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Refer to the SoA (Section 2) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

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

The primary reason for subject withdrawal will be recorded in the eCRF. Primary reasons for withdrawal will be categorized as:

- adverse event
- withdrew consent
- lost to follow-up
- protocol deviation
- lack of efficacy
- subject reached protocol-defined stopping criteria
- study closed/terminated
- investigator discretion

Specific regard should be given to distinguishing withdrawals due to an adverse event, lack of efficacy and protocol deviation. Participant compliance with study treatment during the 12-Week Double-Blind Treatment Period will be assessed as described in Section 7.6.1.

8.3. Lost to Follow Up

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

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

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

the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA (Section 2).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed the following:

- Males:
  - Main Study: approximately 189 mL (including blood samples for genetic research and biomarkers)
  - PK Sub-group: approximately 199 mL (including the above bullet and the serial PK samples)
- Females
  - Main Study: approximately 214 mL (including blood samples for pregnancy testing, genetic research, and biomarkers)
  - PK Sub-group: approximately 224 mL (including the above bullet and the serial PK samples)

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

The following procedures must be completed to ensure that the participant is eligible for the study:

- Obtain informed written consent
- Review inclusion/exclusion criteria, including concomitant medications.
- Full source documentation for the above qualifying procedures and related results are required.
- Any protocol-specified study qualification procedures not already done as part of routine care will need to be conducted after the participant signs the ICF and before randomization.
- The results of all study qualification procedures, whether performed as part of routine care or as a study-specific procedure, are required to assess participant inclusion/exclusion criteria and should, if possible, be available prior to randomization.
- For prompt assessment of the participant's eligibility local laboratory samples should be taken at Screening and the results received and reviewed prior to randomisation to allow review of exclusion criteria 18. It is important that a sample for analysis by the central laboratory is obtained at the same time and promptly sent to the central laboratory. The local lab results will not be entered into the CRF; however, they will be filed in the respective participant's source documentation.
- Samples for Hepatitis B surface antigen, Hepatitis C virus antibody, and HIV antibody will be submitted to the central laboratory **only** for analysis and do not need to be submitted to the local laboratory. Participants who are otherwise eligible may be randomized prior to the receipt and review of these results. If the result for one or more of these parameters is positive, then the participant will need to be withdrawn from the study. Therefore, it is important that a detailed medical history is performed at Screening (Visit 1), in order to minimize the potential for randomization of participants who are positive for one or more of these parameters.
- Those samples taken prior to or at the time of randomization and sent to the central laboratory will serve as the baseline for assessment of potential treatment effect (see the Schedule of Activities in Section 2).
- The screening process ends when randomization occurs. Randomization and first dose of the double-blind study treatment administration should take place as soon as possible following diagnosis of acute moderate/severe exacerbation of COPD and completion of the EXACT-PRO questionnaire and FEV_1 measurement and no later than 48hrs after start of SoC.

9.1. Efficacy Assessments

Efficacy will be assessed via spirometry assessments, subsequent exacerbations of COPD, and patient-reported outcomes (PROs). PRO assessments carried out at study

visits will be completed as the first assessment in the visit schedule before spirometry or any other study procedure.

9.1.1. Spirometry Testing

Spirometry assessments will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS [Miller, 2005]. All participating sites will use standardized spirometry equipment provided by an external vendor contracted by GSK.

All participants will perform lung function maneuvers to assess FEV_1, and FVC at each study visit. For each testing session, at least 3 valid spirometry efforts should be attempted (with no more than 8) using the ATS guidelines [Miller, 2005]. The highest FEV_1 from the valid forced expiratory curves for each testing session will be used.

Protocol-specified spirometry will be performed in the morning (i.e., initiated between 6:00AM and 12:00PM) during visits when clinic FEV_1 is performed as shown in the SoA (Section 2). In addition, protocol-specified clinic FEV_1 must be completed in accordance with the lifestyle restrictions as defined in Section 6.3.1- Section 6.3.5.

During Visits 2 through Visit 6, spirometry will be performed prior to administering double-blind study medication at two time points: pre-bronchodilator (albuterol [salbutamol)] and post-bronchodilator. Post-bronchodilator FEV_1 will be conducted approximately 10 to 30 minutes after the participant-administers 4 inhalations of albuterol (salbutamol) via MDI (i.e., total of 400 mcg) using a spacer/valved-holding chamber or via one nebulized treatment. It is anticipated that participants who are enrolled into the study will receive albuterol as part of the routine treatment of AECOPD during visit 2. In this instance, spirometry should be scheduled to coincide with this treatment to allow post-bronchodilator recordings to be measured. During Visits 6-9, spirometry will be performed prior to administering maintenance COPD medication(s) at two time points: pre-bronchodilator (albuterol [salbutamol)] and post-bronchodilator (as defined above).

Rescue albuterol [salbutamol] should be withheld for 4hrs prior to spirometry measurements, where possible. Usual daily COPD medications should be withheld on the morning of spirometry assessments, where possible.

Baseline Clinic Visit FEV_1 is defined as the post-bronchodilator FEV_1 performed at Visit 2.

Spirometry assessments should be made as close to the scheduled time points as possible. Where multiple assessments are scheduled at the same time point, the sequence of assessments should ideally be as shown below. However, during the Screening Visit (Visit 1) and/or the Randomization Visit (Visit 2), this order may be modified as needed, including instances where some or all of these procedures are performed as part of routine/urgent/emergency/inpatient hospitalized care.

1. Vital signs

2. 12-lead ECG

3. Blood sampling

4. Spirometry assessment

Details regarding the spirometric procedures are provided in the instruction manual provided by the external vendor.

9.1.2. COPD Exacerbation

Following recovery of the index exacerbation, COPD exacerbation assessments will be performed throughout the 12-week treatment period and the 12-week post treatment follow up period at study visits and using the eDiary data.

Additional details on guidelines for COPD exacerbation identification, categorization, reporting and treatment are provided in Section 12.9.5.

9.1.3. Patient-Reported Outcomes (PRO)

Participants will complete the following PROs during this study:

- Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO) (which includes the Evaluating Respiratory Symptoms in COPD [E-RS: COPD] subscales of the EXACT-PRO) at randomization and every evening following day of randomization,
- St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) as defined in the SOA (Section 2).
- COPD Assessment Test (CAT) as defined in the SOA (Section 2). CAT will also be triggered to appear in the e-dairy on the evening following EXACT-defined recovery from the index acute moderate or severe exacerbation of COPD.

For participants who are hospitalized, if a participant is too ill to complete the PRO questionnaires without assistance on a given day, a member of the study staff may verbally recite the questions verbatim to the participant and the staff member may enter the participant's verbal response in the eDiary. The participant's confirmation of the accuracy of the staff member's transcription will be documented in the source document/eDiary. Hospitalized participants will be encouraged to complete the eDiary personally as soon as possible and will be trained to do so before discharge.

9.1.3.1. EXAcerbations of Chronic Pulmonary Disease Tool Patient (EXACT-PRO and Evaluating Respiratory Symptoms in COPD (E-RS: COPD)

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO) is a 14-item, PRO instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in patients with COPD. EXACT-PRO captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient [Leidy, 2011].

The instrument is to be completed every evening (typically at bedtime) using an eDiary. However, at Visit 2 (Randomization) only, the EXACT-PRO is to be completed as the first assessment before randomization and hence will be completed in the morning . Participants will be trained to complete the eDiary before completing the first EXACT assessment.

The daily recording of information allows an assessment of the underlying day to day variability of a patient's symptoms and facilitates the detection of symptom worsening indicative of a COPD exacerbation. The total score for EXACT-PRO ranges from 0 – 100. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the patient becomes more familiar with the tool and the eDiary).

The Evaluating Respiratory Symptoms in COPD (E-RS: COPD) consists of 11 items from the 14-item EXACT-PRO instrument. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e., breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS has a scoring range of 0-40 [Leidy, 2014].

Three subscales of the E-RS: COPD are used to describe different symptoms; dyspnoea, cough and sputum and chest symptoms.

Additional details are provided in the SRM/vendor manual.

In addition to the collection of EXACT-PRO, subjects will also complete daily diary questions to provide the information on other symptoms suggestive of exacerbation: sputum purulence (color), wheezing, sore throat, colds (nasal discharge and/or nasal congestion) and fever without other cause.

9.1.3.2. COPD Assessment Test (CAT)

COPD-related health status will be assessed using the CAT at the visits noted in the SoA (Section 2). The CAT will be administered on the eDiary.

Participants will complete the CAT at relevant study visits, prior to performing any other study procedures (including concurrent medication assessment, adverse event assessment, clinic spirometry, etc.), and prior to completion of the SGRQ-C.

The CAT (www.CATestonline.org) is a validated, short and simple patient-completed questionnaire, which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is designed to measure overall COPD-related health status for the assessment and long-term follow-up of individual patients.

The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, participants rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40 [Jones, 2009; Jones, 2012].

Additional details are provided in the SRM/vendor manual.

9.1.3.3. St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C)

Health-related quality of life will be assessed using the SGRQ-C at the visits noted in the SoA (Section 2). The SGRQ-C will be administered on the eDiary.

Participants will complete the SGRQ-C at relevant study visits, prior to performing any other study procedures (including concurrent medication assessment, adverse event assessment, clinic spirometry, etc.), but after completion of the CAT.

The SGRQ-C is a COPD-specific questionnaire designed to measure the impact of COPD and its treatment on the subject's health-related quality of life [Meguro, 2006]. As well as producing an overall summary score, scores for the individual domains of symptoms, activity and impacts are also produced. It has been used in studies of COPD subjects and has been translated and validated for use in most major languages. The SGRQ-C is derived from the original SGRQ, and produces scores equivalent to the SGRQ instrument [Meguro, 2006]. Research has demonstrated that it is sensitive to change and interpretation of the results has been enhanced by determination of the score change necessary to achieve a clinically meaningful improvement in quality of life [Jones, 2005].

The SGRQ-C is self-completed by participants. It is recommended that the SGRQ-C should be conducted at the same time during each applicable visit (see the SoA [Section 2]). Adequate time (at least 20 minutes) should be allowed, although the participant will not be given any stated or implied time limit for completing the questionnaire. The investigator/designee will ask the participant to complete the questionnaire as accurately as possible. If the participant requests help or clarification of any question in the questionnaire, the investigator/designee is to instruct the participant to re-read the instructions to give the best answer possible. The investigator/designee will not supply the participant with an answer to any question.

Additional details are provided in the SRM/vendor manual.

9.1.3.4. Rescue Medication Use

Participants' use of study-supplied rescue medication (albuterol [salbutamol]) will be captured via the clip-on Propeller Sensor for MDI (for countries where the Propeller Sensor for MDI is available) or via the eDiary (for countries where the Propeller Sensor for MDI is not available or for participants who are supplied nebulized albuterol [salbutamol]). For the nebulized formulation, the number of nebulized treatments over the previous 24 hours will be recorded daily in the eDiary.

For participants who are hospitalized and the clip-on Propeller Sensor for MDI is not available and/or if the participant is too ill to complete the eDiary on his/her own on a given day, a member of the study staff may enter the participant's use of non-nebulized rescue medication or the number of nebulized treatments over the previous 24 hours in the eDiary as applicable. The participant's confirmation of the accuracy of the staff member's transcription will be documented in the eDiary/source document. Additional details are provided in the SRM/vendor manual.

9.2. Adverse Events

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

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

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

- All SAEs will be collected from the start of study treatment until Visit 9 in the Post-Treatment Follow-Up Period, at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- All AEs will be collected from the start of double-blind study treatment until Visit 9 in the Post-Treatment Follow-Up Period at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee as soon as possible and not more than 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. Adverse Events of Special Interest (AESI) – Post-Inhalation Cough Immediately Following Dosing

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 GSK2269557 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 GSK2269557 1000 mcg group, the events of cough for 20 of the subjects were considered by the Investigator to be related to study treatment. From the review of reported events, 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 GSK2269557 DISKUS 1000 mcg QD group) discontinued the study due to cough. Additional details are provided in the Nemiralisib (GSK2269557) Investigator's Brochure.

Therefore, to further evaluate this finding of post-inhalation cough immediately following dosing, during study Visits 2-6 in the 12-Week Double-Blind Treatment Period, Investigators (or medically qualified designees) will monitor participants for potential study treatment tolerability issues, including post-inhalation cough, **within 5 minutes immediately following dosing**. If tolerability issues, including coughing are observed, details will be recorded in the source documentation and eCRF.

The iSRC will have study oversight to ensure that it meets the highest standards of ethics and participant safety and to carry out the planned interim safety data analyses/data reviews as discussed in Appendix 3 and Section 10.3.5. Data (including adverse event reports of post-inhalation cough immediately following study treatment dosing) will be reviewed by the iSRC on a periodic basis, as defined in the iSRC Charter.

9.2.6. Cardiovascular and Death Events

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

The CV eCRFs 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 eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF 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.

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

The following disease related events (DREs) are common in participants with COPD and can be serious/life threatening:

- exacerbation of COPD

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a SAE). These events will be recorded on the DRE page, in this study the exacerbation page in the participant's eCRF within 72 hours after the Investigator becomes aware of the event. These DREs will be monitored by a Safety Review Team (SRT) on a routine basis.

NOTE: However, if either of the following conditions apply, then the event must be recorded and reported as an SAE (See Section 9.2):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or*

- *The investigator considers that there is a reasonable possibility that the event is related to study treatment*

If an exacerbation is caused by pneumonia this must be recorded as pneumonia in the AE or SAE form in the eCRF and the pneumonia form in the eCRF (See Section 9.1.2).

9.2.8. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 14 days after the last dose of study treatment.
- 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, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5 Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.9. Medical Device Incidents (Including Malfunctions)

Medical devices, the study-supplied valved-holding chamber and the clip-on Propeller Sensors to be attached to the double-blind study treatment ELLIPTA inhalers and the study-supplied albuterol [salbutamol] MDIs, are being provided for use in this study for the purposes of standardizing the conduct of the post-bronchodilator FEV_1 measurements and capturing compliance with double-blind study treatment and rescue albuterol [salbutamol] use, respectively. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 8.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Appendix 4 of the protocol.

9.2.9.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 8.

9.2.9.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9). This applies to all participants, including those who discontinue study treatment or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.2.9.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the sponsor by eCRF. If eCRF is unavailable, then completion of the paper Medical Device Incident Form should be utilized.
- The same individual will be the contact for the receipt of medical device reports and SAE.

9.2.9.4. Regulatory Reporting Requirements for Medical Device Incidents

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

9.3. Treatment of Overdose

An overdose is defined as a dose greater than the doses described in Section 7.1 which results in clinical signs and symptoms. In event of an overdose the participants should be closely monitored for AEs/SAEs and these should be recorded in the eCRF.

GSK does not recommend specific treatment for an overdose for nemiralisib.

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

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Physical Examinations

- A complete physical examination will be performed at Screening (Visit 1) and will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems. Height and weight will also be measured and recorded as specified in the SoA (Section 2).
- A brief physical examination will be performed at all other visits and will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs (pulse rate, blood pressure [systolic and diastolic] and respiratory rate) will be performed as specified in the SoA (Section 2), prior to the spirometry maneuvers and with the participant in the sitting position. The participant must be seated at least 5 minutes before these measurements are performed and a single set of values will be collected.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- The vital sign results will be captured in the participant's clinic notes and in the eCRF

9.4.3. Electrocardiograms

Standardized ECG equipment and centralized overreads of the ECGs will be provided to all participating sites by the external provider contracted by GSK.

A 12-lead ECG with a 15-second rhythm strip will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

- For this study, the same QT correction formula (Fridericia's) *must* be used throughout the study for all participants. Safety ECGs and other non-protocol specified ECGs are an exception.
- All ECG measurements will be performed with the participant resting in a supine position for approximately 5 minutes before each reading, which should be carried out after measurement of vital signs and before spirometry.

- The investigator, a designated sub-investigator, or other appropriately trained site personnel, will be responsible for performing the 12-lead ECG recording at each applicable study visit (see SoA [Section 2]).
- All ECGs will be electronically transmitted to an independent cardiologist (contracted by GSK) and evaluated. The independent cardiologist, blinded to treatment assignment, will be responsible for providing measurements of heart rate, QT intervals and an interpretation of all ECGs collected in this study. These results will be provided to the investigator. The investigator is responsible for reviewing ECG reports and attesting to his/her review of the independent cardiologist's assessment.
- A local ECG may be used to assess eligibility criteria however an ECG for central review should also be performed at screening/randomisation. If the central review indicates that the patient is ineligible the patient will be withdrawn from the study.
- Participants with an abnormal ECG reading(s) (exclusionary and non-exclusionary) will be followed/referred to a specialist according to the discretion of the Investigator.
- Details of all cardiac monitoring procedures will be provided by the centralized cardiology service provider.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of routine, non-fasting clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency. At the discretion of the investigator, additional samples may be taken for safety reasons.
- Approximately 40 mL (approximately 8 teaspoons [4 teaspoons each for local laboratory and central laboratory assessment]) of whole blood will be collected at Screening and then approximately 10 mL (approximately 2 teaspoons) of whole blood will be collected at each of the other assessment visits for a total of approximately 100 mL (20 teaspoons) over the course of the study
- All protocol-required clinical laboratory samples will be analyzed by a central laboratory contracted by GSK.
- At screening, for prompt assessment of the participant's eligibility local laboratory samples, with the exception of hepatitis B, hepatitis C, and HIV, should be taken and the results received and reviwed prior to randomisation to allow review of exclusion 18. It is important that a sample for analysis by the central laboratory is obtained at the same time and promptly sent to the central laboratory. The local lab results will not be entered into the CRF; however, they will be filed in the respective participant's source documentation.
- The investigator must review the laboratory report (local [as applicable] and central), document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of double-blind study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator, then this should be documented in the source notes, and in the eCRF where applicable (eg, SAE or AE or dose modification).

9.4.5. Medical Problems and Concomitant Medications

Participants will be instructed to record any medical problems they may have experienced and any medications used to treat those problems over the previous 24 hours in the eDiary. These entries will be reviewed by the Investigator/study coordinator at each study visit and recorded in the eCRF as adverse events and concomitant medications as appropriate. Signs and symptoms of COPD should be evaluated according to Section 9.1.2 and Section 12.9.5.

9.5. Pharmacokinetics

- During the 12-Week Double-Blind Treatment Period approximately 2 mL of whole blood samples for measurement of plasma concentrations of nemiralisib will be collected in a subset of randomized participants (approximately 300) at selected sites on days 14 and 28 (total of 12mL) as below:
    - pre-dose (trough)
    - approximately 0-1 hour post dose
    - approximately >1 hour to 6 hours post dose
- Plasma samples will be analyzed to determine plasma pharmacokinetics. Instructions for the collection and handling of biological samples will be provided by the central laboratory. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of nemiralisib. Samples collected for analyses of nemiralisib plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

- Plasma analysis for nemiralisib will be performed under the control Bioanalysis, Immunogenicity, Biomarkers, BIB /Third Party Resourcing, TPR, GlaxoSmithKline

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

9.6. Pharmacodynamics

See Section 9.8, Section 9.9, and Section 10.3.4 for details of pharmacodynamics.

9.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Central Laboratory Instruction Manual.

9.8. Biomarkers

- For exploratory research, blood samples will be collected for analysis of selected blood inflammatory biomarkers (including but not limited to high sensitivity C-reactive protein [hs-CRP], chemokine interferon-γ inducible protein 10 kDa (CXCL10)], and procalcitonin) in relation to acute exacerbations of COPD.
- Approximately 20 mL (4 teaspoons) of blood will be collected for all participants at each visit noted in the SoA (Section 2). At Visit 1 (Screening), the sample should be collected as soon as possible after the participant has completed the informed consent, PRO assessments and ECG.
- All biomarker samples will be shipped to the central laboratory contracted by GSK/BIB/TPR, GlaxoSmithKline for analysis and reporting.
- All biomarker assessments must be conducted in accordance with the central laboratory manual.

9.9. Spontaneous Sputum

At Screening and Day 56 only, a spontaneous sputum sample will be collected for all participants who are willing and able to provide spontaneous sputum. Sample collection kits and instructions will be provided by the central laboratory contracted by GSK.

9.10. Health Care Resource Utilization (HCRU) and Health Economics

Participants will record (Yes or No) in the eDiary each day whether or not they have had **any** Unscheduled Health Care Contacts (HCRU) contacts/visits for any reason (including COPD-related and non-COPD-related) other than a scheduled visit to the Investigator's site (this includes contacts/visits with/to a physician's office, visits to urgent care, visits to an emergency department, hospitalizations, and inpatient hospitalization days). For any "Yes" response, participants will be prompted to contact the Investigator to promptly report further details regarding the HCRU and the Investigator will receive an e-mail notification as well. The investigator (or designee) will enter the HCRU details in the eCRF. The investigator (or designee) will ask the participant if any of the health care contacts were due to a COPD exacerbation. The investigator (or designee) could refer to his/her records to verify or supplement information given by the participant, if necessary.

Also, at Visits 2-9 or the Early Withdrawal Visit, the resource utilization data reported by the participant for all health care contacts experienced since the last visit will be reviewed by the investigator (or designee).

All confirmed mild, moderate or severe COPD exacerbations will be recorded in the source document and on the COPD Exacerbation form in the eCRF and on the SAE form in the eCRF (if applicable).

The data collected may be used to conduct exploratory analyses of HCRU and other economic analyses and could include:

- Number of medical care encounters
- Hospitalizations
- Duration of hospitalization (total days or length of stay)
- Re-hospitalization within 30 days
- Number of Emergency Room [ER] visits

9.11. Smoking Cessation Counseling

During Visits 1 through 9 or Early Withdrawal, participants will be given smoking cessation counselling, which includes advice regarding the following:

- the health effects that smoking may cause
- the health benefits that may result if they stop smoking
- if they do not feel capable of discontinuing smoking that their primary care physician may be able to discuss anti-smoking strategies with them
- that they may discontinue smoking at any time during the study and will not have to be withdrawn from the study if they do so.

The specific information to be discussed with each subject is provided in the SRM.

10. STATISTICAL CONSIDERATIONS

The primary objective of this study is to characterize the dose response of nemiralisib when administered in addition to SoC on change from baseline in Clinic Visit FEV_1 at Day 84 (measured at trough and post-bronchodilator), in participants diagnosed with an acute exacerbation of COPD requiring treatment with oral/systemic corticosteroid(s) (prednisone 40 mg/day or equivalent) for 5 days **and** antibiotic(s) for 7 days; the dose and/or duration of prednisone (40 mg/day or equivalent) and/or the antibiotic can be modified according to the Investigator's/medically qualified designee's judgement or according to local country/institution practice. There are initially six doses of nemiralisib to be investigated in this study; however, one additional dose may be included during the course of the study.

A key secondary objective is to evaluate treatment effect of nemiralisib compared with placebo on the rate of subsequent exacerbation(s) (moderate and severe) over the 12-Week Treatment Period. In order to increase precision around the estimate of the treatment effect from a pair-wise comparison of the rate of subsequent exacerbation(s) of COPD, the sample size will be increased for the 750 mcg dose of nemiralisib and placebo.

10.1. Sample Size Determination

The sample size has been determined by considering the probability of achieving the end of study success criteria for both the primary and key secondary objectives.

Assuming a 20% withdrawal rate, approximately 1,250 participants will be randomized in total into the study to ensure approximately 1,000 participants complete the 12-Week Treatment Period.

Initially, the randomization ratio between placebo and the the six doses (12.5 mcg, 50 mcg, 100 mcg, 250 mcg, 500 mcg, and 750mcg) of nemiralisib will be 3:1:1:1:1:1:3. Randomization will be stratified by index COPD exacerbation severity (moderate or severe) and whether or not the participant will provide PK samples, to ensure a balance across treatments. Table 2 shows the expected sample sizes allocated to the six doses of nemiralisib and placebo at the end of study. These figures are approximate and assume that no further adjustments to the randomization ratio are made. The actual sample sizes at the end of the study may be different, depending upon whether changes are made following the results of the unblinded interim analysis of change from baseline in clinic visit FEV_1.

Table 2 Expected Sample Sizes Allocated to the Five Doses of Nemiralisib and Placebo at the End of the Study

Dose	Number randomized	Number who complete dosing period and provide clinic visit FEV_1 at Day 84
Placebo	340	272
12.5 mcg	114	91
50 mcg	114	91
100 mcg	114	91
250 mcg	114	91
500 mcg	114	91
750 mcg	340	272

10.1.1. Sample Size for Primary Objective: To Characterize the Dose Response of Nemiralisib when Administered in Addition to SoC on Change from Baseline in Clinic Visit FEV_1 at Day 84

Simulations of change from baseline FEV_1 data have been performed to evaluate the probability of achieving end of study success criteria given the estimated sample size for each dose for various assumed scenarios. Three scenarios were considered, each based on different assumptions of the change from baseline FEV_1 for each of the treatment arms. The scenarios are described in Table 3. The estimate of the dose response profile were obtained from fitting a 3-parameter Emax dose response model to simulated change from baseline FEV_1 data for the expected end of study sample size given these assumed true scenarios. A 3 parameter model was used rather than a 4 parameter model to improve the model convergence under simulation conditions. For the purpose of simulations, a frequentist analysis technique was used which should provide analogous results to fitting non-informative prior distributions for all modelling parameters using a Bayesian framework. A baseline and a single post dose observation were simulated for each subject using the bivariate normal distribution, assuming the between participant standard deviation of 300 mL for both time points, and a correlation of 0.7 between them. The average baseline was considered to be 1.383 L. These values were obtained from the PoC Study PII1116678 (a randomised, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of GSK2269557 administered in addition to standard of care in 126 participants diagnosed with an acute exacerbation of COPD). For each simulation, the appropriate number of participants was simulated using the expected sample size completing Day 84 as described in Table 2. For each scenario, 5,000 iterations of simulations were run with each simulation analyzed using proc nlmixed in SAS.

Table 3 Change from Baseline in FEV_1 Assumptions for Three Assumed Scenarios

Dose	Scenario 1	Scenario 2	Scenario 3
Placebo	-20 mL	-20 mL	-20 mL
12.5 mcg	-15 mL	-15 mL	-20 mL
50 mcg	-15 mL	-10 mL	-20 mL
100 mcg	20 mL	10 mL	-15 mL
250 mcg	50 mL	30 mL	-10 mL
500 mcg	80 mL	40 mL	0 mL
750 mcg	80 mL	50 mL	0 mL

Table 4 shows the probability of achieving various criteria under the three assumed scenarios:

Table 4 Probability of Achieving Various Criteria under the Three Assumed Scenarios

Criteria	Scenario 1	Scenario 2	Scenario 3
Observed lowest dose difference from placebo <25 mL[1]	53%	62%	88%
Observing >90% posterior probability that the true difference from placebo for any dose is >0	100%	100%	64%
Observing >90% posterior probability that the true difference from placebo for any dose is >0 with an observed difference from placebo >75 mL[2]	97%	44%	0%

1. 25 mL chosen to represent a 'non efficacious' difference from placebo
2. 75 mL chosen to represent a minimum clinically meaningful difference from placebo

The results of the simulations indicate that the proposed sample size and participant allocation to each dose is adequate to achieve the key end of study success criterion for change from baseline FEV_1, where this success is defined as demonstrating >90% posterior probability that the true difference from placebo for any dose of nemiralisib is greater than 0 for the assumptions used and the true response scenarios considered. Although the probability of achieving the key end of success criterion for the primary endpoint is high for scenarios 1 and 2, the true nature of the dose response profile is

currently unknown. In addition to these simulations, consideration of the probability of achieving the end of study success for the secondary endpoint of reduction in exacerbation rate has also been given.

10.1.2. Sample Size for Key Secondary Objective: To Evaluate Treatment Effect of Nemiralisib Compared with Placebo on the Rate of Exacerbations

The key secondary endpoint of number of exacerbations over the 12-Week treatment period will be analysed using a Bayesian generalized linear model assuming a negative binomial distribution for the underlying exacerbation rate. Non-informative prior distributions will be used for all modelling parameters.

The probability of achieving the end of study success criterion for this secondary endpoint was calculated assuming a placebo exacerbation rate of 0.51 per 12 weeks and dispersion parameter of 3.5, observed in the PoC Study PII116678. With 340 participants in the selected exacerbation dose arm versus 340 participants in the placebo arm, the probability of declaring success (assuming that the true rate reduction over placebo is 25%) is 76%, where success is defined as demonstrating >80% posterior probability that the true rate reduction over placebo is greater than 0%.

Estimates of the variability (dispersion parameter) and placebo exacerbation rate have been taken from PoC Study PII116678, however have large associated uncertainty. The probability of achieving the end of study success criterion has therefore also been calculated using different assumptions for the dispersion and placebo exacerbation rate and are presented in Table 5. The table shows that the probability of achieving the end of study success criteria for the secondary endpoint varies substantially depending on these assumptions. These assumptions will be assessed during the course of the study.

Table 5 Probability of Achieving the End of Study Success Criterion, Assuming a True Rate Reduction over Placebo of 25% under Different Placebo Exacerbation and Dispersion Assumptions

Placebo Rate	Dispersion Parameter		
	3.5	2	1
0.25	68%	73%	77%
0.51	76%	83%	89%
1.00	81%	90%	96%

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants Enrolled (APE) Population	All participants who are screened for eligibility
Modified Intent-to-Treat (MITT)	All randomized participants who receive at least one dose of study treatment. Participants will be analyzed according to the treatment that they were randomised to. The MITT Population will be used for all efficacy summaries.
Per-Protocol (PP) Population	The PP population is comprised of the MITT population, excluding any participants with an important protocol deviation. The PP population will be used to present sensitivity analyses for the primary and key secondary efficacy endpoints.
Safety Population	All randomized participants who receive at least one dose of study treatment. Participants will be analyzed according to the treatment they actually received. The Safety Population will be used for all safety summaries.
Pharmacokinetic (PK) Population	All participants in the MITT Population for whom a pharmacokinetic sample was obtained and analyzed. The PK population will be used for all PK summaries.

In the event one or more investigators are withdrawn from the trial due to concerns over protocol deviations, then a further population will be defined, which will consist of all participants in the MITT population excluding participants from those investigators. This population will be used to perform additional sensitivity analysis for the primary and key secondary efficacy endpoints.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary efficacy endpoint is the change from baseline in trough and post-bronchodilator Clinic Visit FEV_1 at Day 84. The primary intent will be to analyze this data by fitting a Bayesian dose response model. The 4-parameter Emax model will be fitted by first intent; however, should the data not allow for a suitable model fit, then other models may be attempted such

Endpoint	Statistical Analysis Methods
	as the 3-parameter Emax, Log-linear model or similar. The primary model will take the form: Change from baseline FEV_1 = E0 + (Emax*Dose$^{\gamma}$)/(ED50$^{\gamma}$+Dose$^{\gamma}$) Where: E0 = the response at dose = 0 (placebo) Emax = the maximal response ED50 = the dose that yields 50% of the maximal response γ = the slope parameter Non-informative prior distributions will be fitted to all modeling parameters, ensuring that they are non-informative within the parameter space. Functional uniform priors will be attempted to be fitted by first intent however other prior distributions may be considered. Full details of the specification of prior distributions will be documented in the RAP. The posterior mean change from baseline, along with 95% Credible Intervals, will be presented for each of the studied doses along with the placebo corrected results obtained from the non-linear model. Graphical representation of the dose response across the full dose range will also be produced to allow inference to be made for the non-studied doses based upon the model fit. Posterior probabilities that the true improvement is greater than 0 mL, 50 mL and 100 mL will also be presented. Full details of the statistical analysis will be documented in the RAP.
Secondary	The key secondary endpoint of number of exacerbations (moderate and severe) over the 12-Week treatment period will be analysed using a Bayesian generalized linear model assuming a negative binomial distribution for the underlying exacerbation rate with a log link and an offset to account for the length of time in study for each participant. Non-informative priors will be used for all modelling assumptions. The exacerbation rates for the selected nemiralisib dose and placebo arms, along with the ratio in exacerbation rates nemiralisib/placebo, will be estimated and corresponding 95% credible intervals produced.
Exploratory	Will be described in the RAP

10.3.2. Safety Analyses

Safety endpoints will be summarized by treatment group and all safety analyses will be performed on the Safety Population. Further details will be described in the RAP.

10.3.3. Population PK

A population non-linear mixed effects analysis or other appropriate method(s) will be performed on the sparse plasma samples using an optimal population PK model to describe the time course of systemic exposure of nemiralisib in this target subject population and associated inter- and residual variability. A covariate analysis will be undertaken to evaluate any subject factors (including demographic, physiological, co-medication, pharmacogenetic markers) likely to influence the systemic exposure to nemiralisib in this participant population. Appropriate validation of this population analysis will be performed in line with the European and US regulatory guidance documents on population PK analysis [EMEA- CHMP/EWP/185990/06, 2008 and the FDA, 1999]. Full details of analysis will be provided in the RAP.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

A longitudinal population dose-FEV_1 response analysis will be undertaken using trough FEV_1 at all measured time points over the duration of the study. Quantification of dose–response relationship, covariate effects, and time courses such as placebo effect onset, disease progression, and dose-related effect onset and offset will be characterized if data are amenable. This analysis may provide additional support for dose selection in future studies.

In addition, an exposure-driven clinical safety analysis will be performed using participant-specific exposure data and corresponding systemic safety signals, if data allow. If data are amenable, any relationship between steady state individual average drug levels (Css) with corresponding PROs will be assessed.

The above analysis will be conducted in alignment with the FDA and ICH E4 guidance documents [FDA Guidance for Industry. Exposure-Response relationships- Study Design, Data Analysis, and Regulatory Applications. FDA, Rockville, MD, April 2003 (FDA, 2003), Dose Response Information to Support Drug Registration- ICH E4, 1994]. Full details of analysis will be provided in the Reporting and Analysis Plan (RAP).

10.3.5. Interim Analyses

Interim analyses will be performed during the course of the study.

Interim analyses of the primary endpoint of change from baseline in clinic visit FEV_1 at Day 84 will be performed to determine whether or not any adjustments to the randomization ratio across the nemiralisib doses would help optimize the characterization of the dose response profile. Adjustments could include starting randomization to a nemiralisib dose of 25 mcg QD and/or ceasing randomization to an existing dose(s) of nemiralisib and/or modification of the allocation ratios for the existing nemiralisib doses. Change from baseline in clinic visit FEV_1 will be analyzed by fitting a Baysesian Emax dose response model, as described in Section 10.3.1. The timing of interim analyses of FEV_1 will be pre-specified in the RAP, prior to any unblinding taking place.

In addition, interim analyses will be used to assess the study for futility, to amend the stratification proportions by index exacerbation severity status (moderate or severe) and

to assess the study endpoint assumptions made prior to the study. The specific details regarding the interim analyses will be documented, prior to any un-blinding taking place, in the RAP. The timing of these analyses will depend upon recruitment and may be performed at the same time as the interim analyses of change from baseline FEV_1.

Additionally, an unblinded interim analysis will be conducted at the end of the 12-week treatment period to inform internal program-related decision making.

All interim analyses will be based on un-blinded data and will be performed by the study statistics and programming team (see Section 7.4). The randomization schedules and unblinded datasets will be stored on internal restricted drives. The GSK study team, with the exception of the statistics and programming team, will not have access to an un-blinded copy of the randomization schedule during the course of the trial.

The full details of the interim analyses will be pre-defined in the RAP.

11. REFERENCES

Angulo I, Vadas O, Garçon F, Banham-Hall E, et al. Phosphoinositide 3-kinase δ gene mutation predisposes to respiratory infection and airway damage. Science. 2013;342(6160):866-71.

Barnes PJ. Chronic obstructive pulmonary disease *12: New treatments for COPD. Thorax. 2003;58:803–8.

Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, Connell C, Jemal A, Lee TA, Miravitlles M, Aldington S, Beasley R. Epidemiology and costs of chronic obstructive pulmonary disease. Eur Respir J. 2006;27(1):188-207.

Corral-Gudino L, Jorge-Sánchez RJ, García-Aparicio J, Herrero-Herrero JI, López-Bernús A, Borao-Cengotita-Bengoa M, Martín-González JI, Moreiro-Barroso MT. Use of noninvasive ventilation on internal wards for elderly patients with limitations to respiratory care: a cohort study. Eur J Clin Invest. 2011;41(1):59-69.

Darnell K, Dwivedi AK, Weng Z, and Panos RJ. Disproportionate utilization of healthcare resources among veterans with COPD: a retrospective analysis of factors associated with COPD healthcare cost. Cost Effectiveness and Resource Allocation. 2013;11(13): 1-10.

Donaldson GC, Wedzicha JA. COPD exacerbations 1: Epidemiology. Thorax. 2006;61(2):164-8.

Dose Response Information to Support Drug Registration- ICH E4 Harmonised Tripartite guideline 1994.

European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. CPMP/EWP/558/95 rev 2, 15 December 2011. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003417.pdf

European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infection. EMA/CHMP/351889/2013, 01 May 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500153953.pdf

Fallah MP. Role of PI3K-ACT pathway in the age associated decline in TLR mediated activation of innate and adaptive immune responses.2011. University of Kentucky Doctoral Dissertations. 205. http://uknowledge.uky.edu/gradschool_diss/205.

FDA Guidance for Industry. Exposure-Response relationships- Study Design, Data Analysis, and Regulatory Applications. FDA, Rockville, MD, April 2003.

Food and Drug Administration (FDA). Guidance for industry on acute bacterial exacerbations of chronic bronchitis in patients with chronic obstructive pulmonary disease: developing antimicrobial drugs for treatment. Silver Spring, MD: Center for Drug Evaluation and Research (CDER); 2012. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070935.pdf

George SN, Garcha DS, Mackay AJ, Patel AR, Singh R, Sapsford RJ, Donaldson GC, Wedzicha JA. Human rhinovirus infection during naturally occurring COPD exacerbations. Eur Respir J. 2014 Jul;44(1):87-96.

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2017. Available from: www.ginaasthma.org

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, (2017 Report). Available from: www.goldcopd.org

Guidance for Industry: Population Pharmacokinetics. U.S Department of Health and Human Services, FDA, Washington, DC, 1999.

Guidelines on Reporting the Results of Population Pharmacokinetic Analyses – Committee for Medicinal Products for Human Use - CHMP/EWP/185990/06. Adoption By Chmp 21 June 2007, Date For Coming Into Effect 1 January 2008

Hachad H, Raqueneau-Majlessi I, Levy R. A useful tool for drug interaction evaluation: The University of Washington Metabolism and Transport Drug Interaction Database. Human Genomics. 2010; 5(1): 61-72

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, et al. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;179(5):369-74.

Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, MacNee W, Calverley P, Rennard S, D., Wouters EFM, and Wedzicha JA, for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. N Engl J Med 2010; 363:1128-38.

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

Jones PW. St George's Respiratory Questionnaire: MCID. Journal of COPD. 2005;2:75-79.

Jones, P., Harding, G., Berry, P., Wiklund, I., Chen, W-H., Leidy, N. Development and first validation of the COPD Assessment Test (CAT) Eur Respir J. 2009;34:648–654.

Jones, P., Harding, G., Wiklund, I., Berry, P., Tabberer, M., Yu, R., Leidy, N. Tests of the Responsiveness of the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) Following Acute Exacerbation and Pulmonary Rehabilitation. Chest. 2012;142:134-40

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

Leidy, NK, Sexton, CC, Jones PW, et al Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. Thorax. 2014; 69:443–49.

Leidy, NK, Wilcox, TK, Jones, PW et al. Standardizing Measurement of Chronic Obstructive Pulmonary Disease Exacerbations Reliability and Validity of a Patient-reported Diary. Am J Respir Crit Care Med. 2011;183:323–29.

Lucas CL, Kuehn HS, Zhao F, Niemela JE, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency. Nat Immunol. 2014;15(1):88-97.

MacDonald VM and Gibson PG. To define is to limit: perspectives on asthma–COPD overlap syndrome and personalised medicine. Eur Respir J. 2017; 49: 1-3.

McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. Chest. 2007;132(6):1748-55.

Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved COPD-specific version of the St George's Respiratory Questionnaire. Chest 2006;132: 456-63.

Miller MR, Hankinson J, Odencrantz J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright R, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standarisation of spirometry. Eur Respir J. 2005;26:319-38.

Miravitlles M, Soler-Cataluña JJ, Calle M, Soriano JB. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. Eur Respir J. 2013;41(6):1252-6.

Morris AC, Brittan M, Wilkinson TS, McAuley DF, et al. C5a-mediated neutrophil dysfunction is RhoA-dependent and predicts infection in critically ill patients. Blood. 2011;12;117(19):5178-88.

National Center for Health Statistics. Health, United States 2015 with Special Feature on Racial and Ethnic Health Disparities. Hyattsville, MD: US Dept. Health and Human Services; 2016. (http://www.cdc.gov/nchs/hus/).

Okkenhaug K, Ali K and Vanhaesebroeck B. Antigen receptor signalling: A distinctive role for the p110δ isoform of PI3K. Trends in Immunology, 2007; 28: 80-7.

Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri LM, Johnston SL. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med. 2006;173(10):1114-21.

Pinheiro J, Bretz F, and Branson M. (2006) Analysis of dose-response studies: Modeling approaches. In: *Dose Finding in Drug Development*. Ting, N. (ed.), Springer, New York, pp. 146-171.

Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR). Report 2016.

Sadhu C, Dick K, Tino WT, Staunton DE. Selective role of PI3K delta in neutrophil inflammatory responses. Biochem Biophys Res Commun. 2003; 308(4): 764-769.

Sapey E, Greenwood H, Walton G, Mann E, Love A, Aaronson N, Insall RH, Stockley RA, and Lord JM. Phosphoinositide 3-kinase inhibition restores neutrophil accuracy in the elderly: toward targeted treatments for immunosenescence. Blood. 2014; 123(2): 239-248.

Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(5):1608-13.

Stark AK, Sriskantharajah S, Hessel EM, and Okkenhaug K. PI3K inhibitors in inflammation, autoimmunity and cancer. Curr Opin Pharmacol. 2015 Aug; 23: 82–91.

Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012;67(11):957-63.

The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

U.S. Food and Drug Administration (FDA). Combating Antibiotic Resistance, FDA Consumer Health Information. Updated November 2011. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm092810.htm FDA

Wedzicha JA, Brill SE, Allinson JP, Donaldson GC. Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. BMC Med. 2013;11(181):1-10.

Weisser SB, McLarren KW, Voglmaier N, van Netten-Thomas CJ, Antov A, Flavell RA, Sly LM. Alternative activation of macrophages by IL-4 requires SHIP degradation. Eur J Immunol. 2011;41(6):1742-53.

Word Health Organization (WHO) Fact Sheet. November 2016.
http://www.who.int/mediacentre/factsheets/fs315/en/

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AB	Antibiotic
AE	Adverse Event
ALT	Alanine Aminotransferase
APDS	Activated Phosphoinositide 3-kinase Delta Syndrome, also referred to as p110delta-Activating mutation causing senescent T cells, Lymphadenopathy and Immunodeficiency (PASLI)
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area Under the Plasma Drug Concentration versus Time Curve
BIB	Bioanalysis, Immunogenicity, Biomarkers
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAT	COPD Assessment Test
CXCL10	Chemokine interferon-γ inducible protein 10 kDa
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum Observed Plasma Drug Concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
cRNA	Complimentary Ribonucleic Acid
CSR	Clinical Study Report
CT	Computed Tomography
CV	Cardiovascular
DRE	Disease Related Event
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
E-RS: COPD	Evaluating Respiratory Symptoms in COPD
ERS	European Respiratory Society
EU	European Union
EXACT-PRO	EXAcerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in One Second
FRC	Functional Residual Capacity

FRI	Functional Respiratory Imaging
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma Glutamyl Transferase
GSK	GlaxoSmithKline
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B Surface Antigen
hcCRP	High-Sensitivity C-Reactive Protein
HCRU	Health Care Resource Utilization
HPLC	High-Performance Liquid Chromatography
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1	Interleukin-1
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
iSRC	Internal Safety Review Committee
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
Kg	Kilogram
Kg/m^2	Kilogram/square meter
LTOT	Long-Term Oxygen Therapy
mcg	Microgram
MDI	Metered-Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MgST	Magnesium Stearate
mL	Milliter
MITT	Modified Intent to Treat
MSDS	Material Safety Data Sheet
NIPPV	Non-Invasive Positive Pressure Ventilation
OCS	Oral Corticosteroid
PI3Kd	Phosphoinositide 3-Kinase Delta
PGx	Pharmacogenetics
PK	Pharmacokinetic
PP	Per Protocol
PRO	Patient-Reported Outcome
QD	Once daily

QTc	Corrected QT Interval
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SCS	Systemic Corticosteroid
SDA	Source Document Agreement
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
siVaw	Specific Imaging Airway Volume
siRaw	Specific imaging Airway Resistance
SoA	Schedule of Activities
SoC	Standard of Care (in this protocol this refers to SoC for the index lesion)
SGRQ-C	St. George's Respiratory Questionnaire for COPD Patients
SRDP	Study Results Dissemination Plan
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Terminal half-life
TLC	Total Lung Capacity
Tmax	Time at Maximum Plasma Concentration
TNF	Tumor Necrosis Factor
TPR	Third Party Resourcing
ULN	Upper Limit of Normal
US	United States of America
WBC	While Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
COPD Assessment Test (CAT)
DISKUS
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
E-RS: COPD
EXACT-PRO
Propeller Sensor
SAS
SGRQ-C

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the central laboratory (Q2 Solutions) for all time points as shown in the SoA (Section 2).
- At Screening, for prompt assessment of the participant's eligibility local laboratory samples, with the exception of Hepatitis B, C and HIV,should be taken and the results received and reviewed prior to randomisation to allow for review of exclusion 18. It is important that a sample for analysis by the central laboratory is obtained at the same time and promptly sent to the central laboratory. The local lab results will not be entered into the CRF; however, they will be filed in the respective participant's source documentation
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Albumin
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] at Screening and to confirm any positive			

Laboratory Assessments	Parameters
	urine pregnancy test • Urine pregnancy test (as needed for women of childbearing potential) at visits as shown in the SoA • Hepatitis B surface antigen [HBsAg] and hepatitis C virus antibody [3] • HIV antibody [3] The results of each local laboratory test will not be entered into the CRF; however, they will be filed in the respective participant's source documentation.

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Serum testing
3. Hepatitis B surface antigen [HBsAg], hepatitis C virus antibody and HIV antibody will be assessed by the central laboratory only and will not be assessed at the local lab.

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

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

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

Data Protection

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

Committees Structure

An iSRC will have study oversight to ensure that it meets the highest standards of ethics and participant safety and to carry out the planned interim safety data analyses/data reviews. Data will be reviewed by the iSRC on a periodic basis, as defined in the iSRC Charter. The iSRC, which will comprise a minimum of 3 people (including an independent statistician, an independent clinician with experience in respiratory and general medicine), will be authorized to review unblinded interim safety analyses/data during the study. .

The unblinded interim analysis and periodic safety updates will be performed and delivered to the iSRC by an independent statistician/statistical team. Following review of the interim results for safety, the iSRC will give a recommendation to the pre-specified GSK personnel as to whether or not any adjustments in the study design or conduct should be made, including any adjustments in the treatment allocations. The designated GSK personnel will decide whether or not to act on this recommendation.

Membership, functions and operating procedures of the iSRC for this study will be defined in the iSRC Charter, which is available upon request. Operating procedures for the iSRC will be established before the first review of unblinded data.

Publication Policy

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

Dissemination of Clinical Study Data

Study information from this protocol will be posted on publicly accessible clinical trial registers (e.g., www.clinicaltrials.gov; www.clinicaltrialsregister.eu) before enrollment of subjects begins.

The results summary will be posted to the publicly accessible GSK Clinical Study Register and other publicly available clinical trials registers (e.g.,www.clinicaltrials.gov; www.clinicaltrialsregister.eu) in accordance with GSK policy and SOPs.

In addition, a manuscript will be submitted to a peer-reviewed journal for publication in accordance with GSK policy and SOPs; see also Publication Policy section in this protocol.

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 each participating investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

GSK will provide each participating investigator with the randomization codes for his/her site only after completion of the full statistical analysis.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct

normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

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

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 7.

Table 7 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 10 days, corresponding to time needed to eliminate study treatment (5 half-lives), after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test conducted at Screening (Visit 1).
- Additional pregnancy testing should be performed at Visit 4 (Day 28), Visit 5 (Day 56), and Visit 6 (Day 84; 24 hours after the last dose of double-blind study

treatment) or Early Withdrawal during the 12-Week Double-Blind Treatment Period and at Study Day 112 (Day 28 in the Post-Treatment Follow-Up Period), corresponding to time needed to eliminate study treatment (5 half-lives = 10 days) after the last dose of study treatment and as required locally.

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed and assayed in the central laboratory

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. This applies only to male participants who receive double-blind study treatment.
- 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.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, 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 participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, 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 5. 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 participant who becomes pregnant while participating

- will discontinue study treatment and will be withdrawn from the study.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to nemiralisib or COPD and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to nemiralisib or study treatments of this drug class, and COPD. Genetic research may consist of the analysis of one or more candidate genes (including but not limited to: *PIK3CD*, *PIK3CA*, *IL10*, *CHRNA3*, *CHRNA5*, *DNAH5*, *SUMF1*, and *CELSR1*) or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples may be analyzed to help understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to nemiralisib or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on nemiralisib (or study treatments of this class) or COPD continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

12.7.1. Phase II Liver Chemistry Stopping Criteria

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 SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) • Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted (refer to Section 8.1.8.1 Section 12.7) • If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments (may include if applicable details on required follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Blood sample for pharmacokinetic (PK) analysis, obtained within 14 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 form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form

MONITORING: For bilirubin or INR criteria: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline	For bilirubin or INR criteria: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies

• A specialist or hepatology consultation is recommended • For All other criteria: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). NOTE: not required in China • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3xULN and bilirubin ≥2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. 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 participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

12.7.2. 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 participant safety. • Participant can continue study treatment • Participant 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 participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline

12.8. Appendix 8: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 9.2.9 for the list of GSK medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

12.9. Appendix 9: Guidelines for COPD Exacerbation Identification, Categorization, Reporting, and Treatment

12.9.1. Guidelines for Identifying an Acute Exacerbation of COPD

For this protocol, eligible participants must have an acute exacerbation of COPD requiring an escalation in therapy to include oral/systemic corticosteroid(s) **and** antibiotic(s) as defined in Inclusion Criterion 4.

Acute exacerbation is to be confirmed by an experienced physician and to represent a recent worsening in at least two major and one minor symptoms, one major and two minor symptoms, or all 3 major symptoms.

a. Major symptoms:

   i. Subjective increase in dyspnea

   ii. Increase in sputum volume

   iii. Change in sputum color

b. Minor symptoms:

   i Increased cough

   ii. Increased wheeze

   iii. Sore throat

   iv. Colds (nasal discharge and/or nasal congestion)

   v. Fever (oral temperature >37.5 °C) without other cause

12.9.2. COPD Exacerbation Severity

For the purposes of this study, each COPD exacerbation (including the index exacerbation at Screening and subsequent exacerbation[s]) will be categorized based upon the GOLD [GOLD, 2017] classification of severity as follows:

- **Mild COPD exacerbation:** Worsening symptoms of COPD treated with short-acting bronchodilators (SABDs) only
- **Moderate COPD exacerbation:** worsening symptoms of COPD treated with SABDs plus antibiotics **and/or** oral/systemic corticosteroids
- **Severe COPD exacerbation:** worsening symptoms of COPD that require hospitalization or visit to the emergency room. Severe exacerbation may also be associated with acute respiratory failure.

For this study, mild, moderate and severe exacerbations of COPD will be captured in the eCRF (See Section 12.9.4.).

Note: Use of oral/systemic corticosteroids and antibiotics for the treatment of upper or lower respiratory tract infections will not be considered a COPD exacerbation unless the participant experiences worsening symptoms of COPD, which match the definition of an exacerbation as given above.

12.9.3. Subsequent COPD Exacerbation(s)

After the index exacerbation of COPD at Screening (Visit 1) has resolved, any randomized participant who experiences worsening of COPD for >48 hours should:

- Contact his/her study investigator and/or research coordinator immediately, and report to the study clinic as required
- If the participant is unable to contact his/her study investigator and/or research coordinator, he/she should contact his/her primary care physician (or other health care practitioner as required) and contact their study site as soon as possible
- Continue to complete the eDiary
- If the participant seeks emergent/acute care for worsening respiratory symptoms, he/she should inform the caring Health Care Provider (HCP) to contact the investigator as soon as possible.

Participants with presence of worsening respiratory symptoms will be classified by the Investigator as having:

- A mild/moderate/severe COPD exacerbation and/or pneumonia
- A lower respiratory tract infection (LRTI) [i.e., other than pneumonia]
- Background variability of COPD
- A non-respiratory-related disease
- Other respiratory-related disease

Investigators and site/hospital staff should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations (See Section 12.9.7).

If, based upon these criteria, a participant's symptoms do not fulfil the diagnosis of a COPD exacerbation and/or pneumonia, then the investigator should use his/her clinical judgment to assess the participant's symptoms (including increased volume of sputum production and/or change in the sputum color) for a diagnosis of LRTI (e.g., acute bronchitis), background variability of COPD, a non-respiratory-related disease or other

respiratory-related disease. Investigator judgment should be used in deciding whether to report the signs and symptoms (and/or determined diagnosis) as an AE/SAE in the eCRF.

12.9.4. Collection of COPD Exacerbation Data

COPD exacerbations (mild, moderate, severe) will be collected for all participants who are randomized and receive at least one dose of double-blind study treatment (Visit 2). The time period for collection of exacerbations will begin with the index exacerbation at Visit 1 (Screening) and will end when Visit 9 (last study visit) has been completed.

COPD exacerbations are considered DREs (see Section 9.2.7). Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a SAE). These events will be recorded on the DRE page, in this study the exacerbation page in the participant's eCRF within 72 hours after the Investigator becomes aware of the event. These DREs will be monitored by a Safety Review Team (SRT) on a routine basis

NOTE: However, if either of the following conditions apply, then the event must be recorded and reported as an SAE (See Section 9.2):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or*
- *The investigator considers that there is a reasonable possibility that the event is related to study treatment*

If an exacerbation is caused by pneumonia then pneumonia should be considered the event and must be recorded in the AE or SAE form in the eCRF and on the pneumonia form in the eCRF (See Section 9.1.2)

12.9.4.1. Guideline for Determining Exacerbation Onset and Resolution Dates

The date of onset of the exacerbation is the first day (of at least 2 consecutive days) of worsening symptoms of COPD as described in Section 12.9.1.

The date of resolution of the exacerbation should be based upon when the Investigator/treating physician and/or participant determines that the COPD symptoms have returned to pre-exacerbation levels or to a new baseline. In determining this resolution date, consideration should be given to eDiary recordings and/or participant evaluation.

12.9.4.2. Guideline for Assessing Multiple Mild Exacerbations

Two mild exacerbations can be combined into one, per the Investigator's judgement, if a participant's diary reveals that the two mild COPD exacerbations are separated by no more than three exacerbation-free days.

12.9.4.3. Guideline for Assessing Exacerbations that Increase in Severity

If an exacerbation begins as mild, but becomes moderate or severe or begins as moderate and becomes severe, the exacerbation should be captured as one exacerbation and classified by its highest level of severity.

12.9.5. Treatment of COPD Exacerbations

To be eligible for this protocol, at Visit 1 (Screening), participants must present with a moderate or severe (requires hospitalization) acute exacerbation of COPD requiring treatment with SoC (defined for this protocol as treatment with oral/systemic corticosteroid[s] **and** antibiotic[s]) to be confirmed by an experienced physician (referred to as the 'index COPD exacerbation;' See Inclusion Criterion 4). SoC must be documented in the participant's source documentation and in the eCRF.

For the index COPD exacerbation at Screening and any subsequent COPD exacerbation(s) during the study (Screening, 12-Week Double-Blind Treatment Period, and the 12-Week Post-Treatment Follow-Up Period), the Investigator/medically qualified health care personnel should treat the participant's COPD exacerbation as deemed medically appropriate. If medically necessary, the Principal Investigator or other medically qualified health care personnel may stop the participant's double-blind study treatment temporarily in order to treat the COPD exacerbation.

All medications (COPD and non-COPD) used for the treatment of an exacerbation(s) must be recorded in the source documents and in the COPD Exacerbation form in the eCRF.

12.9.6. Guidelines for Distinguishing Between Continuation of an Existing Exacerbation versus a Subsequent New Exacerbation

- Any course of oral/systemic corticosteroids started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation

- Any course of antibiotics started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation

12.9.7. Pneumonia

Participants who develop pneumonia during the 12-Week Double-Blind Treatment Period should discontinue study treatment.

For the purpose of this study, pneumonia is defined as new auscultatory findings compatible with parenchymal lung infection and/or radiographic evidence of parenchymal/air space disease. All suspected cases of pneumonia are encouraged to be confirmed radiographically within 48 hours of diagnosis. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable). Information regarding chest X-ray-confirmed cases of pneumonia will be recorded in the eCRF. Details regarding the information to be captured for pneumonias will be provided in the SRM.

All medications used to treat the pneumonia are to be recorded in the source documentation and in the eCRF.

12.10. Appendix 10: Protocol Amendment History

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

Amendment 01 – Country Amendment – Korea (Document Number 2017N317218_04)	*26-SEPTEMBER-2017*
Amendment 01 – Global Amendment (Non-tracked changes version: document number 2017N317218_03 – to re-insert the missing text shown in bold that was present in the tracked changes version of Amendment 1 (document number 2017N317218_01), but inadvertently missing from the non-tracked changes version of Amendment 1(document number 2017N317218_02) for Exclusion Criterion #6: "6. Other respiratory disorders: A diagnosis of α1-antitrypsin deficiency as the underlying cause of COPD, active tuberculosis, lung cancer, clinically overt ***bronchiectasis (Note: focal bronchiectasis is not exclusionary), sarcoidosis,*** *pulmonary fibrosis (Note: focal fibrotic pulmonary lesions are not exclusionary), primary pulmonary hypertension, interstitial lung diseases, or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the subject or affect the interpretation of the results."*	*26-SEPTEMBER-2017*
Amendment 01 – Global Amendment (Non-tracked changes version: document number 2017N317218_02)	*15-SEPTEMBER-2017*
Amendment 01 – Global Amendment (Tracked changes version: document number 2017N317218_01)	*24-AUGUST-2017*
Original Protocol (document number 2017N317218_00)	*15-JUNE-2017*

Amendment 1 Country Specific Amendment – South Korea (26Sep17)

Overall Rationale for the Amendment: The rationale for this country-specific Amendment 1 for participating Investigators in South Korea only (Amendment 1/SKO-1) is to include a new Appendix (Appendix 11) to provide information regarding the name, model number and manufacturer for the standardized equipment that is being provided for capturing the electrocardiogram (ECG) data and spirometry data (MasterScope CT) and the sensors for capturing compliance with study-provided, double-blind study treatment (Propeller Sensor for ELLIPTA) and the use of study-provided, rescue medication (Propeller Sensor for MDI) to support importation of these devices into South Korea. This information is also provided in the study documentation provided to all participating Investigators globally by the respective vendor.

This protocol amendment applies to all participating Investigators in South Korea only.

Section # and Name	Description of Change	Brief Rationale
Appendix 11 – new country-specific Appendix for South	New country-specific Appendix (Appendix 11) added for Investigators participating in	To support importation of these devices into South Korea.

Section # and Name	Description of Change	Brief Rationale
Korea only added	South Korea to provide information regarding the name, model number and manufacturer for the standardized equipment that is being provided for capturing the electrocardiogram (ECG) data and spirometry data (MasterScope CT) and the sensors for capturing compliance with study-provided, double-blind study treatment (Propeller Sensor for ELLIPTA) and the use of study-provided, rescue medication (Propeller Sensor for MDI).	
Appendix 12: Protocol Amendment History	Appendix number revised from 11 to 12.	Appendix number revised in light of the addition of the new Appendix 11: Country-Specific Amendment 1 for South Korea (SKO-1).
Table of Contents	The Table of Contents was revised to account for the addition of the new Appendix 11: Country-Specific Amendment 1 for South Korea (SKO-1) and the resulting change in appendix number for the Protocol Amendment History from Appendix number 11 to Appendix number12.	Table of Contents revised in light of the addition of the new Appendix 11: Country-Specific Amendment 1 for South Korea (SKO-1).
Appendix 1: Abbreviations and Trademarks	MasterScope added to the list of trademarks not owned by the GlaxoSmithKline group of companies in the country-specific amendment for South Korea.	MasterScope appears in the new country-specific Appendix 11.

Amendment 1 – Global Amendment (26Sep17):

Overall Rationale for the Amendment: The rationale for Amendment 01 was to incorporate the following revisions to the protocol in response to the Grounds for Non-Acceptance (GNA) issued during the Voluntary Harmonisation Procedure (VHP) in the European Union (EU) as well as other clarifications as summarized in the table below.

This protocol amendment applied to all participating Investigators globally.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities (SOA) 12-Week Double-Blind Treatment Period	Addition of the row titled, "Dispense eDiary and initiate training module within," during Visit 2.	To ensure clarity that the eDiary (which includes the EXACT, CAT and SGRQ questionnaires, etc., already noted in the SOA) is dispensed during Visit 2.
Section 2 Schedule of Activities (SOA) 12-Week Double-Blind Treatment Period and 12-Week Post-Treatment Follow-Up Period	Addition of the rows titled, "Review eDiary" and "Collect eDiary)	To ensure clarity that the eDiary (which includes the EXACT, CAT and SGRQ questionnaires, etc., already noted in the SOA) is to be reviewed during the 12-Week Double-Blind Treatment Period and the 12-Week Post-Treatment Follow-Up Period and collected during Visit 9 or the Early Withdrawal Visit (if Early Withdrawal from the study occurs during either the 12-Week Double-Blind Treatment Period or during the 12-Week Post-Treatment Follow-Up Period)
Section 2 Schedule of Activities (SOA) 12-Week Double-Blind Treatment Period and Section 6.2 Exclusion Criteria, Criterion 22 HIV antibody	Addition of the requirement for HIV testing at Screening;	Since subjects with HIV infection are excluded from the study, it was requested that a specific test to assess the seronegativity to the virus should be performed at Screening.
Section 2 Schedule of Activities (SOA) 12-Week Double-Blind Treatment Period, Early Withdrawal Visit	Addition of "X[19]" in the row titled," Assessment of study treatment compliance"	To correct an inadvertent typographical error.
Section 2 Schedule of Activities (SoA): 12-Week Post-Treatment Follow-Up Period, row for EXACT	Extension of the width of the bidirectional arrow	To ensure clarity that EXACT is completed daily in the evening during the 12-Week Post-Treatment Follow-Up Period.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities (SOA) 12-Week Double-Blind Treatment Period and 12-Week Post-Treatment Follow-Up Period and Section 9.10 Health Care Research Utlization (HCRU) and Health Economics	Revision of text to clarify that participants will record a "Yes" or "No" response in the eDiary each day regarding whether or not they have had any HCRU contacts/visits for any reason (including COPD-related and non-COPD-related) other than a scheduled visit to the Investigator's site. For any "Yes" response, participants will be prompted to contact the Investigator to promptly report further details regarding the HCRU and the Investigator will receive an e-mail notification as well. The investigator (or designee) will enter the HCRU details in the eCRF. Addition of the row titled, "Health Care Resource Utilization (HCRU) Review" during the 12-Week Double-Blind Treatment Period and the Post-Treatment Follow-Up Period, including Early Withdrawal (if applicable).	To clarify that the participant will enter a "Yes" or "No" response in the eDiary and contact the Investigator to report the details, which will be recorded in the eCRF.
Section 3.2 Background and Section 11 References	Addition of a brief summary regarding the reported rate of moderate and severe exacerbations, the prevalence of 'frequent exacerbators' and addition of the corresponding references.	To provide information regarding the estimated frequency of moderate or severe acute exacerbation in patients with COPD, the prevalence of "frequent exacerbators" and the annual rate of rehospitalisation in patients with COPD
Section 6.1 Inclusion Criteria, Criterion 1 Age	Addition of an upper age limit (80 years of age)	To provide an upper age limit for eligible participants, since the safety and efficacy of nemiralisib has not been investigated in the very elderly to date.
Section 6.2 Exclusion Criteria, Criterion 6 Other respiratory disorders	Deletion of inadvertent duplicate text, "active tuberculosis, lung cancer, bronchiectasis (Note: focal bronchiectasis is not exclusionary)"	To delete inadvertent typographical error of duplicated text

Section # and Name	Description of Change	Brief Rationale
Section 6.2 Exclusion Criteria, Criterion 13	Addition of information to provide clarification regarding allowed/excluded strong inhibitors and sensitive narrow therapeutic index substrates of CYP3A4	To provide information about the absence of *in vivo* elimination information and that the role of CYP3A as an important drug metabolising enzyme is based upon *in vitro* data and to revise Exclusion Criterion 13 to more clearly explain which strong inhibitors and sensitive narrow therapeutic index substrates of CYP3A are allowed/excluded. Strong inhibitor inclusion/ exclusion criteria based on GSK2269557 safety margin.
Section 6.4 Screen Failures	Correction of the text regarding re-screened participants will retain the same participant number to must be assigned a new participant number and will be entered into the eCRF again.	To correct an inadvertent typographical error.
Section 7.4 Blinding	Deletion of text regarding Investigator encouraged to contact the GSK Medical Monitor or appropriate GSK study personnel before the treatment blind is broken and replacing with guidance that GSK must be notified of the decision to unblind.	The text encouraging the Investigators to contact/consult with the GSK Medical Monitor or appropriate GSK personnel before making a decision to break the treatment blind was deleted, since breaking of the treatment blind is the responsibility of the Investigator or treating physician in the case of an emergency, or if, in the opinion of the Investigator, it is in the participant's best interest for the Investigator to know the study treatment assignment (consistent with the Declaration of Helsinki and ICH GCP). The deleted text was replaced with text stating that GSK must be notified of the decision to unblind.