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

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

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-

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.

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.

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

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

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.

9.2.3. 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.

- 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.

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

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

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

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.

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

• 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.

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

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]		←==========→					

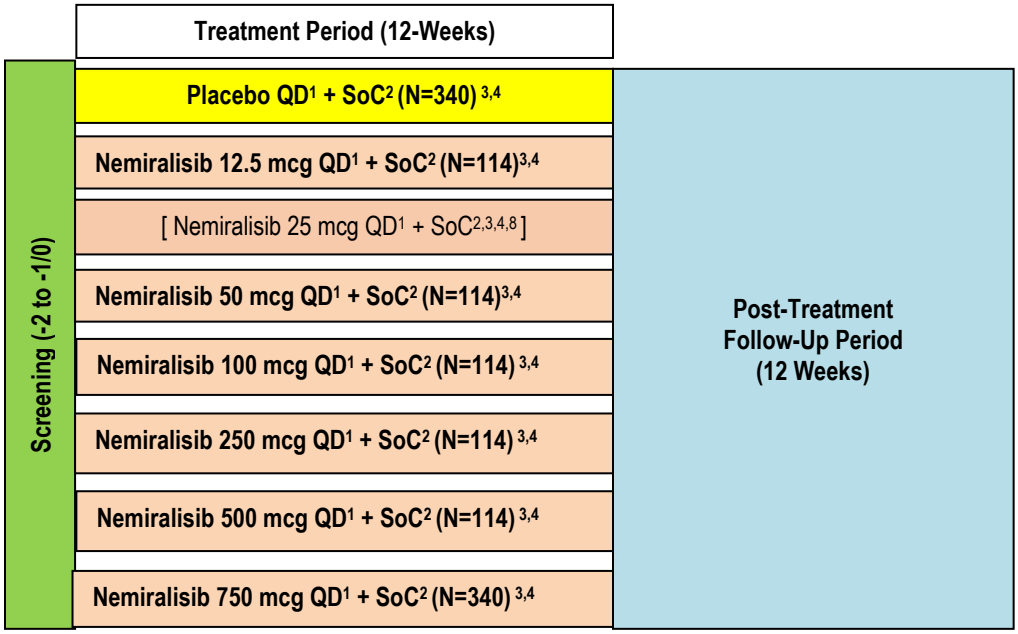
AM=morning; CAT=COPD Assessment Test; CV=cardiovascular; EXACT=EXAcerbations of Chronic Pulmonary Disease Tool; FEV_1=forced expiratory volume in one second; HIV=Human Immunodeficiency Virus; IRT=Interactive Response Technology; PGx=pharmacogentics research; PK=pharmacokinetic; WOCBP=women of child-bearing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

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

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

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

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.

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].

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.

9.2.9.2. 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.

- 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.

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%

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.

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

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E-RS: COPD
EXACT-PRO
Propeller Sensor
SAS
SGRQ-C

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

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

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