Tertiary

- To assess the use of EXACT-PRO for determining the end date of AECOPD.
- To evaluate the load of bacterial and viral pathogens in stable COPD and during AECOPD.
- To collect biological specimens for future respiratory disease-related testing:
  - Aliquots of sputum samples for assay development and microbiome analysis at stable visits and during exacerbation.
  - Blood sampling for potential identification/quantification of biomarkers at Visit 1 and Visit 3.

Rationale for the study

Because the infectious aetiology of AECOPD has been suggested to vary according to geographical region, the primary purpose of this study (which will be conducted in several countries in Asia Pacific) is to evaluate the occurrence of potential bacterial and viral pathogens in the sputum of stable COPD patients and at the time of AECOPD. Given the increasing and projected burden of COPD in the Asia Pacific region, this study will also evaluate the frequency, severity and duration of AECOPD, as well as the impact of AECOPD on health-related quality of life (HRQOL), healthcare utilisation and lung function.

In addition, both PCR and bacteriological methods will be used for characterisation (quantification in some cases) of bacteria in sputum. To date, identification of bacteria and assessment of bacterial load is done in the vast majority of cases by culture. However, the few studies that have compared culture with PCR demonstrated that PCR is more discriminatory at detecting typical airway bacteria [Curran, 2007; Singh 2014]. Moreover, in a multi-centre study, PCR has the advantage that it can be performed on stored sputum samples, and can therefore be done centrally, whereas culture has to be performed on fresh sputum samples, which can lead to variable results due to variability in testing methods between laboratories.

Epoch	Epoch 001			
Type of contact	**Screening Visit**	**Visit 1**	**Visit 2**	**Visit 3**
Time point	**Pre-Month 0**	**Month 0**	**Month 6**	**Month 12**
Blood samples for biomarkers		●		●
Record Adverse Events (AEs)* ^	●	●	●	●
Record serious adverse events (SAEs) ^	●	●	●	●
Screening conclusion	●			
Study conclusion				●
HRQOL questionnaires:				
CAT		O	O	O
SGRQ-C		O	O	O

● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
[a] For non-eligible subjects, only informed consent, inclusion/ exclusion criteria, demographic data and SAEs related to study participation that occurred after signing the informed consent pages need to be completed in the subject's eCRF. For other activities, 'not done' can be indicated.
[b] Record both documented and self-reported, non-documented AECOPD. Subjects need documentation for at least 1 moderate or severe AECOPD within the previous year to be eligible for study participation.
[c] Significant comorbidities include weight loss, cardiovascular disease, hypertension, gastro-oesophageal reflux disease, osteoporosis/ osteopenia, skeletal muscle wasting and dysfunction, anxiety/ depression and diabetes.
[d] To be recorded in the 'Physical examination' section of the eCRF.
[e] Only study certified site staff can perform spirometry assessment.
[f] Only if no chest X-ray is taken within the previous 3 months.
[g] Sputum can be collected spontaneously or can be induced, as per investigator judgement. Sputum sampling should only be done if, in the opinion of the investigator, it is safe for the subject.
[*] Non-serious AEs will be recorded in the eCRF and will not be entered into the safety database.
^ *Refer to Table 10 for description of which AE/SAEs are collected in this study*.
[h] Physical examination ***(Visit1-3)*** should be done only if necessary by the investigator or delegate.

6.4. Detailed description of study procedures

6.4.1. Procedures during the Screening Visit

6.4.1.1. Informed consent

The signed informed consent of the subject must be obtained before study participation during the screening visit. Refer to Section 5.1 for the requirements on how to obtain informed consent.

6.4.1.2. Check inclusion and exclusion criteria

All applicable inclusion and exclusion criteria as described in Sections 4.2 and 4.3 will be checked before enrolment.

6.4.1.3. Record demographic data

Demographic data such as date of birth, gender, geographic ancestry will be recorded in the subject's eCRF.

6.4.1.4. Record medical history

The subject's medical history will be obtained by review of the subject's medical records. Prior to study participation, any pre-existing conditions or signs and/or symptoms present in a subject will be recorded**.**

6.4.1.5. Record AECOPD history within the previous year

Documented, self-reported and non-documented AECOPD should be recorded in the eCRF. However, for study participation the subject should have had at least one documented moderate or severe AECOPD episode within the previous year.

6.4.1.6. Smoking exposure history (ATS-DLD-78A questionnaire)/biomass exposure history (At screening visit only)

The subject will be asked to complete the smoking history questionnaire (which is a shortened version of the American Thoracic Society-Division of Lung Diseases-78A [ATS-DLD-78A] questionnaire) by himself/herself. The subject will have to provide information about his/ her smoking history, including duration (number of years) and number of cigarettes smoked. Subject years exposed to biomass will be assessed from information obtained on indoor exposure to fuels such as wood, crop waste and dung, or coal.

From the information obtained via the questionnaire, calculation of the pack-years will be done for inclusion into the study. Please refer to the SPM for details on how to calculate pack years using this questionnaire and for guidance on administration of the exposure history questionnaire.

Note: Screening visit should ideally occur not more than 6 weeks before visit 1.

- **Epoch 001**: Prospective data collection starting at Screening Visit (Pre-month 0) and ending at Visit 3 (Month 12).

Table 3 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age	Epoch
			Epoch 001
Prospective	Approx 200	≥ 40 years	X

- **Study visits/contacts:**
  - Screening visit.
  - Three scheduled (stable) study visits occurring at 6 months intervals.
  - For each AECOPD: AECOPD visit (within 96 hours of the onset of the symptoms) and follow-up phone call(s) (at least every 2 weeks until the AECOPD has resolved). Follow-up phone contacts will define end of AECOPD.
- **COPD symptoms**

  Subjects will be asked to record their COPD symptoms in an electronic Diary Card on a daily basis:
  - Daily in the morning throughout the study: Morning symptoms questionnaire.
  - Daily at bedtime throughout the study: EXACT-PRO (EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome) questionnaire.
- **Biological samples:**
  - **Sputum samples** collected at site (spontaneous or induced, as per investigator judgement) will be collected at each study visit at the site (scheduled [stable] visits and AECOPD visits) if, in the opinion of the investigator, it is safe for the subject.

Or

  - **Sputum sample collected at subject's home (spontaneous).** Self-collection of the sputum sample will be allowed in specific cases, where the first dose of antibiotics absolutely needs to be taken before an AECOPD visit can take place. This is not allowed at scheduled visits when subject should be in stable condition.

*Note**:** The sputum samples collected during AECOPD should preferably be obtained before administration of the first dose of antibiotics to treat the AECOPD (if applicable).*

  - **Blood samples** for biomarker testing will be collected at Visit 1 (M0) and Visit 3 (M12).

ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
K. pneumoniae	*Klebsiella pneumoniae*
LAR	Legally Acceptable Representative
M. catarrhalis	*Moraxella catarrhalis*
OTC	Over-the-counter
P. aeruginosa	*Pseudomonas aeruginosa*
PCD	Primary Completion Date
PCR	Polymerase chain reaction
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
S. aureus	*Staphylococcus aureus*
S. pneumoniae	*Streptococcus pneumoniae*
SAE	Serious Adverse Event
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SPM	Study Procedures Manual
USA	United States of America

- To describe the severity and duration of all-cause AECOPD, overall and by GOLD grade.
- To assess the impact of all-cause AECOPD on HRQOL.
- To assess the impact of all-cause AECOPD on lung function.
- To assess the impact of all-cause AECOPD on healthcare utilisation.

Refer to Section 9.1.2 for the definition of the secondary endpoints.

2.3. Tertiary objective(s)

- To assess the use of EXACT-PRO for determining the end date of AECOPD.
- To evaluate the load of bacterial and viral pathogen in stable COPD and during AECOPD.
- To collect biological specimens for future respiratory disease-related testing:
  - Aliquots of sputum samples for assay development and microbiome analysis at stable visits and during exacerbation.
  - Blood sampling for potential identification/quantification of biomarkers at Visit 1 and Visit 3.
  - Bacterial isolates for further strain characterisation.

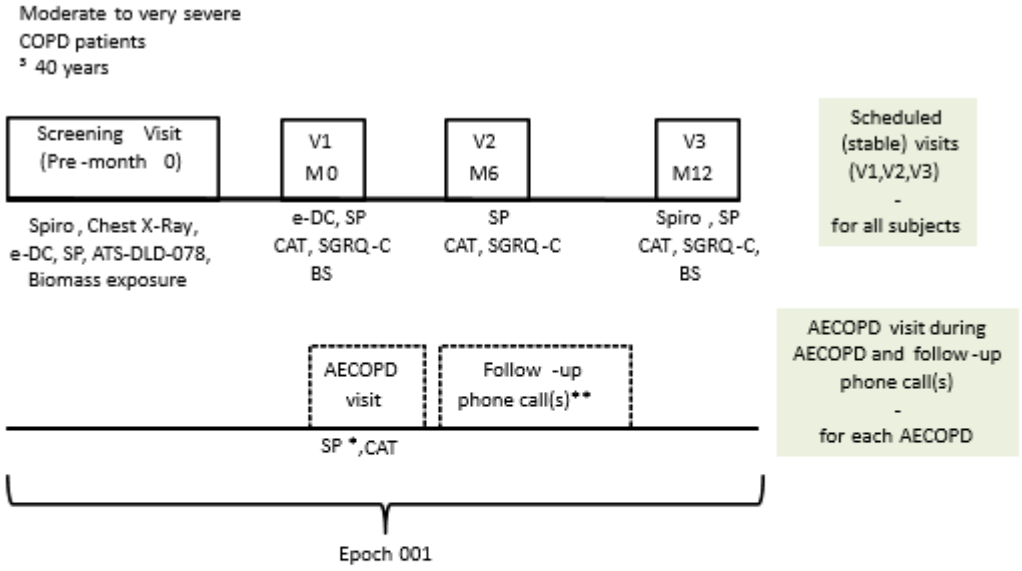
Refer to Section 9.1.3 for the definition of the tertiary endpoints.

3. STUDY DESIGN OVERVIEW

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 6), are essential and required for study conduct.

Figure 2 presents an overview of the study design.

Figure 2 Study design overview



V = Visit; M = Month; SP = sputum sample; e-DC: Training and use of electronic Diary card; CAT = COPD assessment test; SGRQ-C = St. George's Respiratory Questionnaire for COPD patients; spiro = spirometry; BS = Blood Sampling; AECOPD = acute exacerbation of COPD; ATS-DLD-078 = American Thoracic Society and National Heart and Lung Institute-Division of Lung Disease Respiratory Questionnaire

* The sputum samples during AECOPD should preferably be obtained before administration of the first dose of antibiotics to treat the AECOPD (if applicable). Self collection of the sputum sample will be allowed in specific cases, where the first dose of antibiotics absolutely needs to be taken before an AECOPD visit can take place. This is not allowed at scheduled visits when subject should be in stable condition.

** Follow- up phone calls will take place at least every 2 weeks, until the AECOPD has resolved

Type of design: Prospective, epidemiological, interventional, multi-country, cohort study.

- Study population: A cohort of approximately 200 moderate to very severe COPD patients with at least 1 documented moderate or severe AECOPD in the year before enrolment.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF) and electronic diary cards.
- Primary completion Date: Visit 3 (Month 12). Refer to glossary of terms for the definition of PCD.
- End of Study (EoS): Last testing results released of samples collected at Visit 3.
- Duration of the study: The study will last approximately 1 year for each subject from screening visit up to study conclusion.

3.1.1. Detection of AECOPD

Occurrence of potential AECOPD will be monitored by means of electronic Diary Cards which the subject will use to record his/ her morning symptoms on a daily basis. The electronic Diary Cards will be programmed as to detect potential AECOPD as follows (based on the Anthonisen criteria [Anthonisen, 1987]):

- Worsening of two or more of the following major symptoms for at least two consecutive days: dyspnoea, sputum volume, sputum purulence (colour), OR
- Worsening of any major symptom together with any of the following minor symptoms for at least two consecutive days: sore throat, colds (nasal discharge and/or nasal congestion), fever (oral temperature ≥ 37.5°C) without other cause, increased cough, increased wheeze.

Note that: The same two symptoms do not have to be present on both days as long as at least one major symptom is present on both days.

Each time a potential AECOPD is detected via the electronic Diary Card, the device will alert the subject to contact the study site, and at the same time an alert will be sent to the site so that the investigator or medically qualified individual contacts the subject to determine if the alert is an AECOPD or not, and if an AECOPD visit is warranted. In addition, the site should proactively follow-up all data received via the electronic Diary Card and contact the subject whenever deemed necessary.

During the contact with the subject, the investigator or medically qualified individual will determine whether the subject might actually be experiencing an AECOPD (e.g. notifications that can be explained solely by increased physical activity will not be considered):

- If the investigator or medically qualified individual concludes that the subject is not experiencing an AECOPD, this should be documented/ reported in the electronic Diary website (StudyWorks). Please refer to study procedures manual (SPM) for more details on how to perform this.
- If the investigator or medically qualified individual concludes that the subject may be experiencing an AECOPD, an AECOPD visit will be scheduled as soon as possible after the onset of AECOPD symptoms as recorded in the electronic Diary Card or confirmed by the subject (maximum 96 hours after onset of symptoms and, if applicable, preferably before starting treatment with antibiotics). The AECOPD onset date will be captured in the eCRF and additional information about severity will be also collected.
  - In case the AECOPD is confirmed but no AECOPD visit can take place, the site should record the information in the medical records subject files, and in the eCRF in medical records section and obtain all relevant information regarding the AECOPD (hospital record, medical record etc.) and record this in the eCRF.
- If the investigator concludes the subject is experiencing/continuing with the same event for which a visit has been performed already, an AECOPD visit should not take place. Medical treatment should be foreseen according to standard medical practice outside of the study.

6.4.1.7. Smoking status

The subject's smoking status (current or former smoker) will be recorded in the eCRF. Refer to the glossary of terms for the definitions of current and former smoker.

6.4.1.8. Physical examination

At the screening visit, a complete physical examination of the subject will be performed which will include vital signs after at least 10 minutes of rest (systolic/ diastolic blood pressure, heart rate, respiratory rate). Collected information will be recorded in the eCRF.

Treatment of any abnormality observed during a physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

6.4.1.9. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study procedure. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit. The test should be carried out before performing chest x-ray. If the test is positive, the chest x- ray should not be performed and the subject should be withdrawn from the study.

6.4.1.10. Measure/ record height and weight

The height and weight of the subject will be measured and recorded in the 'Physical examination' section of the eCRF.

6.4.1.11. Pre- and post-bronchodilator spirometry

Pre- and post-bronchodilator spirometry should be performed during the screening visit. Only study-certified staff can perform spirometry assessment for this study. Spirometry will be performed following the eResearchTechnology (ERT) instructions for use FlowScreen manual and following all safety requirements.

A good quality spirometry should be obtained, and will be confirmed by the spirometry provider. If during the Screening Visit a good quality spirometry was not obtained, the spirometry can be repeated, as per investigator's medical judgement. If a repeat spirometry is elected, the site should make all possible efforts to repeat the spirometry preferably within 7 days of the previous spirometry. The data will be directly transferred from the provider to GSK Biologicals.

Treatment of any abnormality observed during spirometry has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

6.4.1.12. Chest X-ray

Screening - Baseline test

A posterior to anterior (PA) chest X-ray must be performed at the screening visit if no chest X-ray/ CT scan is available within the last 3 months.

Subjects with evidence of clinically significant abnormalities not believed to be due to the presence of COPD will not be eligible for study participation.

6.4.1.13. Train subjects on the use of electronic Diary Card and assign electronic Diary Card to subject

- From screening visit to visit 1, subjects will be trained on how to use their electronic Diary Card. At visit 1, the investigator should evaluate whether or not the subject will be able to comply with the daily completion of the electronic Diary Card throughout the study. Compliance with electronic Diary Card completion implies that subject learns how to translate his/ her respiratory symptoms in answers to the questions as well as acquiring the technical expertise to use the device. Refer to the SPM for recommendations on what is considered adequate compliance.
- The site staff will follow electronic Diary Card completion closely and should provide timely input/guidance to ensure that the subject correctly completes the eDiary Card both AM & PM as per protocol.

In addition, site staff will pro-actively monitor electronic Diary Card compliance throughout the study and provide the necessary input to maintain compliance.

6.4.1.14. Sputum sampling (Amended 19 October 2018)

- Sputum samples will be collected during the screening visit if, in the opinion of the investigator, it is safe for the subject. If it is not safe, the sputum sample will not be collected and the subject will not be included in the study.
- Sputum samples can be either spontaneous or induced, as per investigator judgement. Internal standard operating procedures should be put in place to ensure proper sputum collection, sample tracking and subject safety at study collection site.
- At home, sputum collection will not be permitted.
- Collected sputum will be diluted in DTT, processed and cultured within 6hrs of collection for microbiology testing.
- Remaining DTT-sputum will be aliquoted as such. These samples will be kept at -70/80°C until shipment to GSK or GSK designated lab for testing.

Refer to the SPM and the Central Laboratory Investigator Manual for more details and guidance on handling of sputum samples.

eCRF at study visit. Refer to the SPM for more details and guidance on recording of healthcare use.

6.4.2.12. Additional treatments prescribed by primary and secondary care physician

All treatments prescribed by the primary and secondary healthcare physician will be recorded in the eCRF.

6.4.2.13. Train subjects on the use of electronic Diary Card and assign electronic Diary Card to subject

- From screening visit to visit 1, subjects will be trained on how to use their electronic Diary Card. At visit 1, the investigator should evaluate whether or not the subject will be able to comply with the daily completion of the electronic Diary Card throughout the study. Compliance with electronic Diary Card completion implies that subject learns how to translate his/ her respiratory symptoms in answers to the questions as well as acquiring the technical expertise to use the device. Refer to the SPM for recommendations on what is considered adequate compliance.
- The site staff will follow electronic Diary Card completion closely and should provide timely input/guidance to ensure that the subject reaches the targeted learning curve.

In addition, site staff will pro-actively monitor electronic Diary Card compliance throughout the study and provide the necessary input to maintain compliance.

6.4.2.14. Return the electronic diary card

On the last visit (Visit 3), the site staff will pro-actively check with the subjects on whether he/she has returned the electronic Diary Card.

6.4.2.15. Sputum sampling (Amended 19 October 2018)

- Sputum samples will be collected during the scheduled visits, if in the opinion of the investigator, it is safe for the subject.
- Sputum samples can be either spontaneous or induced, as per investigator judgement. Internal standard operating procedures should be put in place to ensure proper sputum collection, sample tracking and subject safety at study collection site.
- At home, sputum collection will not be permitted.
- Collected sputum will be diluted in DTT, processed and cultured within 6hrs of collection for microbiology testing
- Remaining DTT-sputum will be aliquoted as such. These samples will be kept at -70/80°C until shipment to GSK or GSK designated lab for testing.

Refer to the SPM and the Central Laboratory Investigator Manual for more details and guidance on handling of sputum samples.

6.4.3. Procedures during AECOPD visit

6.4.3.1. Record date of visit

If an AECOPD occurs at of the scheduled study visits, the date of visit should be document in the eCRF.

6.4.3.2. Physical examination

Physical examination at the AECOPD visit will be performed only if deemed necessary by the investigator or delegate.

Treatment of any abnormality observed during a physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

6.4.3.3. Pregnancy Test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study procedure. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit. The test should be carried out before performing chest x-ray. If the test is positive, the chest x- ray should not be performed and the subject should be withdrawn from the study.

6.4.3.4. Chest X-rays/pneumonia confirmation

AECOPD visit test

A chest X-ray should be performed at the AECOPD visit if it is clinically indicated to exclude another cause of worsening of symptoms (*e.g.* new infiltrate for pneumonia cases).

All suspected pneumonias will require confirmation as defined by the presence of new infiltrate(s) on chest x-ray AND at least 2 of the following signs and symptoms:

- Increased cough,
- Increased sputum purulence (colour) or production,
- Auscultatory findings of adventitious sounds (e.g., egophony, bronchial breathing sounds, rales, etc),
- Dyspnea or tachypnea,
- Fever (oral temperature ≥ 37.5 °C),
- Elevated WBC (>10,000/mm3 or >15% immature forms),
- Hypoxemia (HbO2 saturation <88% or at least 2% lower than baseline value),

All incidences of pneumonia must be captured on the pneumonia page of the eCRF.

6.4.4.2. Blood Sampling

Blood sampling: Refer to section 6.4 for the description of sampling procedure.
Full details for the collection, handling, and processing of blood samples are provided in the Module on Biospecimen Management in the SPM and in the Central Laboratory Investigator Manual accompanying this protocol.

6.4.5. Health Related Quality of Life questionnaires

Refer to section 6.4.2 for description of the Quality of Life (QoL) questionnaire. The subject will be asked to complete the HRQOL questionnaires by himself/herself, during specified study visits directly in the electronic Diary Card.

6.4.6. Recording of AEs/SAEs

- Refer sections 6.4.1.15, 6.4.2.18 and 6.4.3.12 for recording of AEs/SAEs.

6.4.7. Study conclusion

Refer section 6.4.2.19 for study conclusion.

6.5. Biological sample handling and analysis

Please refer to the SPM and the Central Laboratory Investigator Manual for details of biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research. In addition, these samples may be used to perform research related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be invited to give another specific consent to allow GSK or a contracted partner to use the samples for future research including development of tests and their quality assurance. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit/contact), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

6.5.1. Use of specified study materials

When materials are provided by GSK Biologicals or the central laboratory, it is MANDATORY that all samples be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals or the central laboratory does not provide material for collecting and storing samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM and Central Laboratory investigator manual.

6.5.2. Biological samples

Table 7 present the biological samples that will be collected for this study.

Table 7 Biological samples

Sample type	Quantity	Unit	Timepoints	Sub-cohort
Fresh Sputum	Maximum possible	ml	Screening visit (Pre-Month 0)	All screened subjects
			• Visit 1 (Month 0) • Visit 2 (Month 6) • Visit 3 (Month 12)	All enrolled subjects
			• AECOPD visit (within 96 hours of onset of symptoms)	
Blood for biomarkers	21	ml	• Visit 1 (Month 0) • Visit 3 (Month 12)	All enrolled subjects

c. Requires hospitalisation or prolongation of an existing hospitalisation,

Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting.

Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an SAE.

d. Results in disability/incapacity,

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

or

e. Is a congenital anomaly/birth defect in the offspring of a study subject

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

7.1.3. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In absence of diagnosis, abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or an SAE (refer to Sections 7.1.1 and 7.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

7.2. Detecting and recording AEs, SAEs

7.2.1. Time periods for detecting and recording AEs and SAEs

AEs and SAEs related to study participation will be collected and recorded from the time of the first study visit until the subject is discharged from the study.

In order to fulfil international reporting obligations, SAEs that are related to study participation (i.e., protocol-mandated procedures, invasive tests, a change from existing therapy) will be collected and recorded from the time the subject consents to participate in the study/study start until she/he is discharged from the study.

AEs leading to withdrawal from the study, will be collected and recorded from the time of the first study visit until the subject is discharged from the study.

An overview of the protocol-required reporting periods for SAEs and AEs leading to withdrawal is given in Table 10.

Table 10 Reporting period for SAE and AEs leading to withdrawal (Amended 19 October 2018)

Study activity	Screening Visit		Visit 1		Visit 2		Visit 3		AECOPD Visit		Study Conclusion
	Pre-Month 0		M 0		M 6		M 12		Within 96 hours of onset symptoms		
AEs/SAEs related to study participation*											
AEs/*SAEs* leading to withdrawal from the study											

Study participation: Specific procedures required by study participation.

7.2.1 will be reported promptly to GSK within the timeframes described in Table 11 once the investigator determines that the event meets the protocol definition of an SAE.

Table 11 Timeframes for submitting SAEs related to study participation to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs related to study participation	24 hours*	Electronic/ Expedited Adverse Event Report	24 hours*	Electronic/ Expedited Adverse Event Report

* Timeframe allowed after receipt or awareness of the information.

7.3.2. Contact information for reporting SAEs to GSK

Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability: GSK Biologicals Clinical Safety & Pharmacovigilance Fax: [redacted] or [redacted]

7.3.3. Completion and transmission of SAEs reports related to study participation to GSK

Once an investigator becomes aware that an SAE has occurred in a study subject, the investigator (or designee) must complete the information in the electronic Expedited Adverse Event Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding an SAE, the report should still be completed within 24 hours. Once additional information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

7.3.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must complete, then date and sign a paper Expedited Adverse Event Report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designee) must complete the electronic Expedited Adverse Event Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic reporting system.

7.3.4. Updating of SAE after freezing of the subject's eCRF

When SAE information is received after freezing of the subject's eCRF, new or updated information should be recorded on a paper Expedited Adverse Event Report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (see the Sponsor Information) within the designated reporting time frames specified in Table 11.

Note: For studies using INFORM, freezing of the subject's eCRF would mean removal of write access in the subject's eCRF.

7.3.5. Regulatory reporting requirements for SAEs

The investigator will promptly report all SAEs to GSK Biologicals in accordance with the procedures detailed in Section 7.3.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under epidemiological investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

9.1.3. Tertiary endpoints

- EXACT-PRO scores in stable COPD patients and during AECOPD, over the course of 1 year.
- Bacterial load measured by both culture and PCR in COPD and during AECOPD.
- HRV load measured by PCR in COPD and during AECOPD.

9.2. Determination of sample size

The primary objective of this study is to describe the proportion of bacterial and viral pathogens (overall and by species) detected in sputum in stable COPD and during AECOPD.

Assuming around 90% of the All Enrolled Set participated in the study, on average 1 AECOPD visit and 80% of the above population set can provide an evaluable sputum sample at AECOPD, for 240, 200, 160, and 50 enrolled subjects, one may expect around 180, 140, 120, 40 sputum samples, respectively. Assuming that results from these sputum samples are independent and that the between country variability is much smaller than the within country variability, we would have the following 95% exact confidence interval for different incidences in sputum samples from exacerbations (see Table 12).

Table 12 Exact 95% confidence intervals of the percentage of occurrence of a specific bacterium from sputum collected during AECOPD

	Number of evaluable sputum samples during AECOPD			
%	N=180	N=140	N=120	N=40
5	[2.3 ; 9.3]	[2.0 ; 10.0]	[1.9 ; 10.6]	[0.6 ; 16.9]
10	[6.0 ; 15.3]	[5.6 ; 16.2]	[5.3 ; 16.8]	[2.8 ; 23.7]
20	[14.4 ; 26.6]	[13.7 ; 27.6]	[13.3 ; 28.3]	[9.1 ; 35.6]
30	[23.4 ; 37.3]	[22.6 ; 38.3]	[22.0 ; 39.0]	[16.6 ; 46.5]
40	[32.8 ; 47.6]	[31.8 ; 48.6]	[31.2 ; 49.3]	[24.9 ; 56.7]
50	[42.5 ; 57.5]	[41.4 ; 58.6]	[40.7 ; 59.3]	[33.8 ; 66.2]

N = total number of evaluable sputum samples during AECOPD.

One of the secondary objectives is to estimate the incidence rate of all-cause AECOPDs in the study population.

Assuming around 80% of the all enrolled set completed the study, for 240, 200, 160 and 50 subjects enrolled, one would have at least 190, 160, 130 and 40 subjects evaluable respectively. Assuming further that around 80% of the subjects can provide an evaluable sputum sample at AECOPD, this would lead to around 150, 130, 100, 30 subjects (see Table 13).

Table 13 95% confidence intervals of AECOPD incidence rates with different overdispersion values

			Φ = 1		Φ = 1.5		Φ = 2	
0.2 AECOPD/ subject/ year			95% CI*		95% CI*		95% CI*	
T	n	Value (n/T)	LL	UL	LL	UL	LL	UL
30	6	0.20	0.04	0.36	0.00	0.40	-0.03	0.43
100	20	0.20	0.11	0.29	0.09	0.31	0.08	0.32
130	26	0.20	0.12	0.28	0.11	0.29	0.09	0.31
150	30	0.20	0.13	0.27	0.11	0.29	0.10	0.30
1 AECOPD/ subject/ year			95% CI*		95% CI*		95% CI*	
T	n	Value (n/T)	LL	UL	LL	UL	LL	UL
40	40	1.00	0.69	1.31	0.62	1.38	0.56	1.44
130	130	1.00	0.83	1.17	0.79	1.21	0.76	1.24
160	160	1.00	0.85	1.15	0.81	1.19	0.78	1.22
190	190	1.00	0.86	1.14	0.83	1.17	0.80	1.20
2 AECOPD/ subject/ year			95% CI*		95% CI*		95% CI*	
T	n	Value (n/T)	LL	UL	LL	UL	LL	UL
40	80	2.00	1.56	2.44	1.46	2.54	1.38	2.62
130	260	2.00	1.76	2.24	1.70	2.30	1.66	2.34
160	320	2.00	1.78	2.22	1.73	2.27	1.69	2.31
190	380	2.00	1.80	2.20	1.75	2.25	1.72	2.28
3 AECOPD/ subject/ year			95% CI*		95% CI*		95% CI*	
T	n	Value (n/T)	LL	UL	LL	UL	LL	UL
40	120	3.00	2.46	3.54	2.34	3.66	2.24	3.76
130	390	3.00	2.70	3.30	2.64	3.36	2.58	3.42
160	480	3.00	2.73	3.27	2.67	3.33	2.62	3.38
190	570	3.00	2.75	3.25	2.70	3.30	2.65	3.35

* Normal approximation with variance = $\Phi\ n/T^2$, where Φ is the overdispersion factor for a Poisson distribution (calculations performed in Microsoft Excel).
T = Total number of evaluable subjects; **n** =Total number of exacerbations; **CI** = confidence interval; **LL** = lower limit; **UL** = upper limit.

9.3. Cohorts for Analyses

The following study cohorts will be evaluated.

9.3.1. All screened Set

The all screened set will include all screened patients.

9.3.2. All Enrolled Set

The all enrolled set will include all successfully screened subjects in the study.

9.6. Analysis of secondary objectives

The proportion of sputum samples obtained at each visit (confirmed stable visits* and AECOPD visits [any severity, mild, moderate and severe]) and positive for specific bacterial pathogens by both bacteriological methods and PCR (overall and by bacterial species) will be computed with 95% confidence intervals.

> * *A confirmed stable visit will be defined as a scheduled study visit for which the investigator confirms in the eCRF that the subject is stable / has recovered from a previous exacerbation.*

The proportion of sputum samples obtained at each stable visit and positive for specific bacterial/viral pathogens by bacteriological methods and PCR, respectively (overall and by bacterial/ viral species) will be computed with 95% confidence intervals, by GOLD grade at enrolment.

The proportion of sputum samples obtained at each AECOPD visits and positive for specific bacterial/ viral pathogens by bacteriological methods and PCR, respectively (overall and by bacterial/viral species) will be computed with 95% confidence intervals, by AECOPD severity.

The proportion of sputum samples obtained at each confirmed stable/AECOPD visit with previous administration of antibiotics or not and positive for specific bacterial/ viral pathogens by bacteriological culture and PCR, respectively (overall and by bacterial/viral species) will be computed with 95% confidence intervals.

The following incidence rates will be computed, with 95% confidence intervals (CI):

- All-cause AECOPD.
- AECOPD having sputum containing bacterial pathogens found by PCR ***or*** by bacteriological methods or by both methods (overall and by, but not limited to, the following bacterial species: *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *S. aureus*, and *P. aeruginosa*).

The 95% CI of the incidence rate will be computed using a model which accounts for repeated events. The Generalised linear model assuming the Negative Binomial distribution for the response variable with logarithm as link function, and the logarithm of time for follow-up as an offset variable will be used. The incidence rates described above will also be computed for mild, moderate severe AECOPD and by GOLD grade at enrolment and will be estimated by country.

The number of subjects that report at least 1 AECOPD will be tabulated and descriptive statistics (median, mean, range, standard deviation, first and third quartiles) on the number of days of AECOPD episodes will be presented, for any, mild, moderate and severe AECOPD.

Descriptive statistics (median, mean, range, standard deviation, first and third quartiles) on the *CAT* and SGRQ-C scores will be tabulated at each respective visit.

Summary statistics (mean, median, standard deviation, maximum and minimum) on post-bronchodilator FEV1% of predicted normal value will be tabulated at each respective visit.

Descriptive summaries on healthcare use will be provided.

9.7. Analysis of tertiary objectives

Descriptive statistics (median, mean, range, standard deviation, first and third quartiles) on the end date of AECOPD as provided by the investigator or estimated by EXACT-PRO (via a specific algorithm which will be detailed in the Statistical Analysis Plan) will be presented.

Descriptive summaries of the quantity of specific bacteria at each scheduled [stable] and exacerbation visit will be provided for both culture and PCR analysis.

Descriptive summaries of the quantity of specific viruses at each scheduled [stable] and exacerbation visit will be provided for PCR analysis.

A conditional logistic model will be fitted to estimate the odds ratio of being in a stable state *vs.* an exacerbation state given the presence or not of several bacterial pathogens found by bacteriological culture and by country. The same model will also be performed for bacterial and viral pathogens found by PCR.

9.8. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

9.8.1. Sequence of analyses

- An interim analysis of the bacterial primary objective will be performed when at least 40 AECOPD sputum samples are available. The rate of positive samples will be computed for Hi, NTHi and Mcat together and per pathogen. No study report will be written at this stage.
- A final analysis of all objectives will be performed after the last subject last visit of the entire study. A final study report will be written at this stage.

9.8.2. Statistical considerations for interim analyses

All analyses are exploratory and will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

10. ADMINISTRATIVE MATTERS

To comply with ICH GCP or other applicable guidelines, administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, ownership, public disclosure requirements and publications must be met.

10.1. Electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

Once the database is archived and the clinical study report is complete and approved by all parties, each participating investigator will be provided with a CD-ROM of the final version of the data generated at his/her investigational site.

10.2. Study monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

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

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

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and

Study design

- Type of design: Prospective, epidemiological, interventional, multi-country, cohort study.
- Study population: A stable cohort of approximately 200 moderate to very severe COPD patients with at least 1 documented moderate or severe AECOPD in the year before enrolment.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF) and electronic diary cards.
- Primary completion Date: Visit 3 (Month 12). Refer to glossary of terms for the definition of PCD.
- End of Study (EoS): Last testing results released of samples collected at Visit 3.
- Duration of the study: The study will last approximately 1 year for each subject.
- Note: Screening visit should ideally occur not more than 6 weeks before visit 1.
- **Epoch 001**: Prospective data collection starting at Screening Visit (Pre-Month 0) and ending at Visit 3 (Month 12).

Synopsis Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
Prospective	Approx 200	≥ 40 years	X

Discussion of study design

The primary objective of this study is to prospectively investigate the prevalence and distribution of bacteria and viruses isolated from sputum samples from moderate to very severe COPD patients and at the time of AECOPD, in Asian populations. In order to increase the chance that the patients will exacerbate during the study, only patients with a documented history of at least 1 moderate or severe AECOPD in the previous year will be recruited, as this is known to be the best predictor of AECOPD [Hurst, 2010]. Therefore, this study will permit an estimation of incidence of AECOPD in a COPD population at increased risk of exacerbation. It will not provide a true population-based incidence of AECOPD.

In order to study factors affecting disease progression in Asia Pacific, prospective data from a relatively large cohort of COPD patients is essential. The use of electronic Diary Cards to detect changes in the respiratory symptoms that define an AECOPD, the standardised questionnaires and spirometry

Table 5 presents the list of study procedures for AECOPD visits.

Table 5 List of study procedures for AECOPD visits

Type of contact	AECOPD Visit	End of AECOPD phone call(s)
Time point	**within 96 hours of onset symptoms**	**at least every 2 weeks as of AECOPD visit until AECOPD has resolved[i]**
Record date of visit	●	
Physical examination[l]	●	
Urine Pregnancy Test	●	
Chest X-rays/pneumonia confirmation[j]	●	
Confirm AECOPD and record its start date	●	
Record current medication for ***AE***COPD	●	
Record healthcare resource utilisation	●	
Record additional COPD treatments prescribed by primary and secondary care physicians		●
Sputum sampling[k]	●	
HRQOL questionnaire:		
CAT	O	
Record AECOPD severity[m]	●	●
Record AECOPD end date		●
Record Adverse Events (AEs)*^	●	●
Record serious adverse events (SAEs)^	●	●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
[i] End of AECOPD phone calls/ visits should be scheduled at least every 2 weeks, until the AECOPD has resolved. Only the last phone call will be recorded in the eCRF as the end of the AECOPD phone call. All intermediate calls should be recorded on source documentation.
[j] Only if clinically indicated to exclude another cause of worsening of symptoms (*e.g.* pneumonia). If a chest X-ray is clinically indicated but a chest X-ray/ CT scan has already been taken for that AECOPD as part of medical care before the study AECOPD visit takes places, the results of that chest X-ray/ CT scan can be used. All cases of pneumonia (including all signs and symptoms assessed to confirm pneumonia) should be documented in the eCRF.
[k] Sputum can be collected spontaneously or can be induced, as per investigator judgement. Sputum sampling should only be done if, in the opinion of the investigator, it is safe for the subject.
[l] Physical examination should be done only if necessary by the investigator or delegate.
[m] AECOPD severity grading as indicated in Table 2.
* Non-serious AEs will be recorded in the eCRF and will not be entered into the safety database.
^ *Refer to Table 10 for description of which AE/SAEs are collected in this study*.

Table 6 presents the intervals between study visits.

Table 6 Intervals between study visits

Interval	Optimal length of interval	Allowed interval[1]
Screening Visit (pre-Month 0)→ Visit 1	± 14 days	≤42 days before Visit 1
	Scheduled study visits	
Visit 1 (Month 0) → Visit 2 (Month 6)	182 days	175 - 203 days
Visit 2 (Month 6) →Visit 3 (Month 12)	182 days	175 - 203 days
AECOPD-driven study visit(s) and/ or phone contacts		
Onset AECOPD symptoms → AECOPD Visit	-	max 96 hours[2]

[1] If an AECOPD occurs at the time one of the scheduled study visits is planned, the stable study visit should be re-scheduled to a later date, when the subject is stable again and within the time window specified. In consultation with GSK, the concluding visit (Visit 3, Month 12) may however exceptionally be conducted outside of the allowed interval if necessary by the investigator.
[2] AECOPD visits will be scheduled as soon as possible after the onset of AECOPD symptoms as recorded in the electronic Diary Card or confirmed by the subject (maximum 96 hours after and, if applicable, preferably before starting treatment with antibiotics).

- **HRQOL assessments**
  - Subjects will be asked to complete the COPD assessment Test (*CAT*) at each study visit (scheduled [stable] visits and AECOPD visits).
  - Subjects will be asked to complete the St. George's Respiratory Questionnaire for COPD patients (SGRQ-C) at each scheduled (stable) study visit (Visit 1 [Month 0], Visit 2 [Month 6] and at Visit 3 [Month 12]).
- Pre- and post-bronchodilator spirometry assessments will be done for all subjects at Screening Visit (pre-Month 0) and at Visit 3 (Month 12).

3.1. Discussion of study design

The primary objective of this study is to prospectively investigate the prevalence and distribution of bacteria and viruses isolated from sputum samples from moderate to very severe COPD patients and at the time of AECOPD, in Asian populations. In order to increase the chance that the patients will exacerbate during the study, only patients with a documented history of at least 1 moderate or severe AECOPD in the previous year will be recruited, as this is known to be the best predictor of AECOPD [Hurst, 2010]. Therefore, this study will permit an estimation of incidence of AECOPD in a COPD population at increased risk of exacerbation. It will not provide a true population-based incidence of AECOPD.

In order to study factors affecting disease progression in Asia Pacific, prospective data from a relatively large cohort of COPD patients is essential. The use of electronic Diary Cards to detect changes in the respiratory symptoms that define an AECOPD, the standardised questionnaires and spirometry assessments will allow robust conclusions to be drawn about the effects of exacerbations on decline in lung function and HRQOL. EXACT PRO will be used to assess breathlessness, cough and presence of sputum, chest symptoms, difficulty bringing up sputum, feeling tired or weak, sleep disturbance, and feeling scared or worried about their condition. Advantages to this approach include standardised data, reduced recall bias, and the potential to identify events and determine resolution based on a predefined scoring algorithm [Leidy, 2011]. Standardised questionnaires completed during study visits include the SGRQ-C and the CAT. The SGRQ-C is designed to assess HRQOL, current health and does not specify a recall period. The CAT is a simple, short, patient-completed instrument to assess HRQOL and symptom burden in patients with COPD. The CAT has good internal consistency and test-retest reliability, correlates strongly with the SGRQ-C, and is able to distinguish between stable patients and those undergoing an AECOPD [Jones, 2012].

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Anonymised data:	Information about an individual that GSK or a third party cannot reasonably attribute to the individual, or could only attribute to the individual by expending a disproportionate amount of time, effort or expense (e.g. de-identified or aggregated information). For the purpose of this policy, Key-Coded personally identifiable information shall not be considered Anonymised Information
Current smoker	A person who is currently smoking or who stopped smoking within the past 6 months.
Cohort study:	A form of epidemiological study where subjects in a study population are classified according to their exposure status/disease and followed over time (prospective/ retrospective) to ascertain the outcome(s).
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.

During the AECOPD visit, the investigator will confirm the occurrence of the AECOPD based on clinical and medical judgement and based on the Anthonisen criteria and will record its date of onset. The end date of the AECOPD and its severity will be determined/ confirmed by the investigator/delegate during (a) follow-up phone call(s), which will take place at least every 2 weeks until the AECOPD has resolved.

If an AECOPD occurs at the time when one of the scheduled [stable] study visits is planned, it should be handled and recorded as an AECOPD visit, with all relevant AECOPD visit study procedures performed and, if possible, the stable study visit should be re-scheduled to a later date, when the subject is stable again and within the time window specified in the protocol.

The investigator/site must engage their best efforts to reach the patients, however, if the site does not succeed in contacting the patient, the reason should be recorded and an explanation given about what occurred. For example, the subject could be hospitalized or could visit a different physician (and in that case medical record should be obtained), or the subject is on holidays or not able to go the site.

3.1.1.1. Date of onset and end date of AECOPD

The date of onset is the first day (of at least 2 consecutive days) of worsening symptoms of COPD, as determined by the Investigator according to the Anthonisen criteria.

The end date should be based on when the investigator determines that the AECOPD symptoms have resolved. In determining this end date, consideration should be given to symptoms recorded in the electronic Diary Card and subject assessment during the phone calls.

Both start and end date of each confirmed AECOPD occurring from the screening visit to study conclusion will be recorded in the eCRF.

3.1.1.2. Guideline for assessing AECOPD that increase in severity

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

6.4.1.15. Recording of AE/SAEs

- Recording of AE/SAEs
- Refer to Section 7.2 for procedures for the investigator to record AE/SAEs. Refer to Section 7.3 for guidelines on how to submit SAE reports to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

6.4.1.16. Screening conclusion

The investigator will review all the data collected during the screening visit to ensure accuracy and completeness.

6.4.2. Procedures during Visit 1, Visit 2 and Visit 3

6.4.2.1. Check inclusion and exclusion criteria

At visit 1, all applicable inclusion and exclusion criteria as described in Sections 4.2 and 4.3 will be checked before enrolment.

6.4.2.2. Record intercurrent comorbidities

Significant comorbidities include, but is not limited to, weight loss, cardiovascular disease, hypertension, gastro-oesophageal reflux disease, osteoporosis/ osteopenia, skeletal muscle wasting and dysfunction, anxiety/ depression and diabetes.

6.4.2.3. Vaccination History

Record in the eCRF whether the subject received any influenza vaccination within the previous 12 months or has ever received any pneumococcal vaccination (including date of vaccination [as detailed as possible]).

6.4.2.4. Smoking status

The subject's smoking status (current or former smoker) will be recorded in the eCRF. Refer to the glossary of terms for the definitions of current and former smoker.

6.4.2.5. Physical examination

Physical examination at each study visit (Visit 1, Visit 2 and Visit 3) will be performed only if deemed necessary by the investigator or delegate.

6.4.2.16. Blood Sampling

- Blood samples for biomarker analysis will be taken at the scheduled visits; Visit 1 (M0) and Visit 3 (M12), including:
  - Hematology profile, including differential cell counts
    - Approximately 2.0 mL of whole blood will be collected for hematology assessment. These samples should be kept at room temperature and shipped on the day of collection, ambient.
  - Specific biomarkers will include serum hsCRP, CXCL10 (IP-10) and plasma fibrinogen, may include other biomarkers based on results of ongoing disease understanding research.
    - Approximately 8.5 mL of whole blood will be collected and processed to serum for hsCRP & CXCL10 (IP-10) assessment. After processing, these samples should be kept at -70/-80°C until shipment.
    - Approximately 4.5 mL of whole blood (Na Citrate) will be collected and processed to plasma for fibrinogen assessment. After processing, these samples should be kept at -70/-80°C until shipment.
    - Approximately 6.0 mL of whole blood (EDTA) will be collected and processed to plasma for other biomarker assessment. After processing, these samples should be kept at -70/-80°C until shipment.

Refer to the SPM and the Central Laboratory Investigator Manual for more details and guidance on the collection, handling, and processing of blood samples.

6.4.2.17. HRQOL questionnaires

- The subject will be asked to complete the HRQOL questionnaires by himself/herself, during specified study visits directly in the electronic Diary Card as detailed in Table 4 and Table 5.
- Refer to the SPM for more details and guidance on the HRQOL questionnaires.

6.4.2.18. Recording of AE/SAEs

- Refer to Section 7.2 for procedures for the investigator to record AE/SAEs. Refer to Section 7.3 for guidelines on how to submit SAE reports to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

6.4.2.19. Study conclusion

The investigator will:

- Review all the data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.

The investigators and site 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. For all suspected cases of pneumonia, investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible.

Please refer to SPM for details on what should be considered for pneumonia confirmation.

6.4.3.5. Confirm AECOPD and record start date

The investigator should confirm the AECOPD based on his/her medical judgement. The date of onset of AECOPD will be determined as detailed in Section 3.1.1.1 and will be documented in the eCRF.

6.4.3.6. Record current medication for AECOPD

- At each study visit/contact, the investigator should question the subject about any medications administered for treatment of AECOPD.
- All medications administered for treatment of AECOPD will be recorded in the eCRF.

6.4.3.7. Record healthcare resource utilisation

Healthcare use will be obtained through review of the subject's medical record (aided by subject self-reporting). Healthcare utilisation includes all unscheduled visits to a physician office, visits to urgent care, visits to emergency department, and hospitalizations. Healthcare use should be recorded in the eDiary Card and reported in the eCRF at study visit. Refer to the SPM for more details and guidance on recording of healthcare use.

6.4.3.8. Additional COPD treatments prescribed by primary and secondary care physician

All treatments prescribed by the primary and secondary healthcare physician will be recorded in the eCRF.

6.4.3.9. Sputum sampling (Amended 19 October 2018)

- Sputum samples during AECOPD should preferably be obtained before administration of the first dose of antibiotics to treat the AECOPD (if applicable). Sputum can be collected spontaneously or can be induced, as per investigator judgement. Sputum sampling should only be done if, in the opinion of the investigator, it is safe for the subject.

6.5.3. Laboratory assays (Amended 19 October 2018)

Please refer to APPENDIX A for the address of the clinical laboratories used for sample analysis.

The quality of sputum samples will be assessed at the investigator's institution and/ or at a laboratory designated by GSK Biologicals by gram staining.

Standard bacteriological methods (and semi-quantitative counts) will be performed on fresh sputum samples at the investigator's institution and/or at a laboratory designated by GSK Biologicals. Identification of potential bacterial pathogens will be performed according to agreed identification methods (potential pathogens including, but not necessarily limited to, *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae* and *A. baumannii*). All results should be entered in the eCRF.

Further bacterial characterization for *H. influenzae* isolates: Identified *H. influenzae* isolates should be collected and stored in the investigator's institution and will undergo further species confirmation (i.e. confirmed *H. influenzae)* and when possible, further differentiation (i.e., Hi/NTHi**)** at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using molecular techniques such as PCR. Identified *H. influenzae* isolates might undergo further testing at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals' using other molecular techniques such as PCR and sequencing.

Identified *M. catarrhalis* isolates should be collected and stored in the investigator's institution and might undergo further species confirmation (and when possible, further differentiation) at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals using molecular techniques such as PCR and sequencing.

Identified *P. aeruginosa* isolates should be collected and stored in the investigator's institution and might potentially undergo further testing at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals.

Further bacterial pathogens identification (including, but not necessarily limited to, *H. influenzae, S. pneumoniae*, *M. catarrhalis*, *S. pyogenes, S. aureus* and *P. aeruginosa*) and quantification (for *H. influenzae, S. pneumoniae, M. catarrhalis*) on stored sputum samples will be performed at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals using qualitative PCR and/or quantitative PCR.

Viral pathogens identification (including, but not necessarily limited to, RSV, parainfluenza virus, enterovirus/ HRV, metapneumovirus, influenza virus, adenovirus, bocavirus and coronavirus) on stored sputum samples will be performed at GSK Biologicals' laboratory or a laboratory designated by GSK Biologicals using multiplex reverse transcription polymerase chain reaction (RT-PCR).

In addition, some respiratory viral pathogens (such as HRV) will be quantified in stored sputum samples (or subset) using RT-PCR at GSK Biologicals' laboratory or at a laboratory designated by GSK Biologicals.

7.2.2. Evaluation of SAEs (Amended 19 October 2018)

7.2.2.1. Active questioning to detect SAEs

Each subject/ will be instructed to contact the investigator immediately should the subject manifest any signs and symptoms (s)he perceives/ they perceive as serious. ***However, an occurrence of severe AECOPD is not defined as an SAE and therefore does not need to be reported as such, unless in the opinion of the Investigator this is related to a study procedure.***

All SAEs either observed by the investigator or his/ her staff or reported by the subject spontaneously or in response to a direct question will be evaluated by the investigator. The nature of each event, date and time of onset, outcome, intensity and possible relationship to the study procedures should be established.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding the AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/ or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

7.2.2.2. Assessment of causality

The investigator should assess the causality of each SAE. The investigator will use clinical judgement to determine the relationship between the SAEs and study participation. Alternative causes, such as natural history of the underlying diseases, other concomitant therapy and other risk factors will be considered and investigated.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly.

If an event meets the criteria to be considered as 'serious' (see section 7.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possibly contributing factors to each SAE.

7.4. Treatment of AEs

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE (that are required to be reported as per protocol should be recorded in the Expedited Adverse Event Report of the subject's eCRF.

8. SUBJECT COMPLETION AND WITHDRAWAL

8.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

8.2. Subject withdrawal

Subjects who are withdrawn because of AEs or SAEs related to study participation must be clearly distinguished from subjects who are withdrawn for other reasons.

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up. The mode of contact will be by telephone. Three phone contacts will be made with an interval of one week between each phone call.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Non-serious AE.
- Protocol violation (specify).
- Consent withdrawal, not due to an AE*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

9.3.3. Full Analysis Set

The Full Analysis Set (FAS) will include all enrolled patients except for those who discontinued the study during Visit 1.

Study objectives will be assessed on the FAS. The population set for each analysis will change according to the subjects evaluable for the specific endpoint.

Note: Subjects using antibiotics on a continual basis (defined as more than 1 month in total) will be allowed to continue study participation, but may be eliminated from the analyses.

9.4. Analysis of demographics

Demographic characteristics (age at enrolment, gender and geographical ancestry) and cohort description will be summarised using descriptive statistics:

- Frequency tables will be generated for categorical variable such as geographical ancestry.
- Mean, median, standard deviation, minimum and maximum will be provided for continuous data such as age.

The distribution of subjects enrolled among the study sites will be tabulated.

Withdrawal status will be summarised according to the reason for withdrawal. The number of withdrawn patients will be tabulated by study visit and overall.

All tables will also be generated by country.

9.5. Analysis of primary objective

The proportion of sputum samples obtained at each visit (confirmed stable visits[*] and AECOPD visits and positive for specific bacterial/ viral pathogens by bacteriological methods and PCR, respectively (overall and by bacterial/viral species) will be computed with 95% confidence intervals.

[*] *A confirmed stable visit will be defined as a scheduled study visit for which the investigator confirms in the eCRF that the subject is stable/ has recovered from a previous exacerbation.*

investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

10.3. Record retention

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

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements or applicable laws or regulations, or GSK standards/procedures otherwise, the minimum retention period will default to 25 years after completion of the study report.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility and transfer of ownership of the records in the event the investigator leaves the site.

10.4. Quality assurance

To ensure compliance with GCP or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.