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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ASTEGOLIMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**
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PLAN PREPARED BY:	[redacted], Ph.D.
	[redacted], Ph.D.
	[redacted], Ph.D.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

SPONSOR:	F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document V 3.0.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
3	see electronic date stamp on last page of this document	V 5.0, 8 November 2024
2	10 March 2025	V 5.0, 8 November 2024
1	7 June 2024	V 4.0, 20 June 2023

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
Section 2.1	Reordered the secondary endpoints in the testing hierarchy	Per the sponsor's re-assessment of clinical interest and historical data
Section 2.2.1 and 4.1	To include all participants enrolled at China sites into primary analysis population	To provide clarification on the analysis population due to accelerated China population enrollment
Section 4.2.2, 4.2.3, 4.3.1.6 and 4.4	An adjustment covariate (the number of moderate or severe COPD exacerbations during the 12 months preceding screening to the study) was included in the main analysis model for the primary endpoint. Similar changes were made for endpoints "Annualized rate of severe COPD exacerbations" and "Annualized rate of moderate COPD exacerbations". The main model specified in SAP version 2 was accordingly redefined as a sensitivity analysis. Sensitivity analyses using Poisson regression models were added accordingly.	The inclusion of a baseline prognostic covariate increases statistical efficiency of the primary model.
Section 4.2.3	Sensitivity analysis using negative binomial and Poisson regression model respectively using baseline SGRQ-C total score as an adjustment variable added	To assess the robustness of the study findings

Additional minor changes have been made throughout to improve clarity and consistency.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AER	annualized exacerbation rates
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CV	coefficient of variation
ECG	electro cardio gram
E-RS:COPD	Evaluating Respiratory Symptoms in COPD
EU	European Union
EXACT	EXAcerbations of Chronic Pulmonary Disease Tool
FEV_1	forced expiratory volume in 1 second
H_a	alternative hypothesis
H_0	null hypothesis
HRQoL	health-related quality of life
iDMC	independent Data Monitoring Committee
IxRS	interactive voice/web-based response system
mITT	modified intent-to-treat
PD	Pharmacodynamic
PK	Pharmacokinetic
Q2W	once every 2 weeks
Q4W	once every 4 weeks
RCRM	Random Coefficient Regression Model
RR	rate ratio
SAP	Statistical Analysis Plan
SC	subcutaneous
SGRQ-C	St. George's Respiratory Questionnaire-COPD
SOC	standard of care
sST2	soluble ST2
VAS	Visual Analog Scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) details the planned analyses and statistical methods for Study GB44332. The analyses described in this SAP will supersede those specified in Protocol GB44332 for the purposes of a regulatory filing.

1.1 TRIAL OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This Study GB44332 will evaluate the efficacy and safety of astegolimab compared with placebo in participants with chronic obstructive pulmonary disease (COPD) who are former or current smokers and have a history of frequent exacerbations. Table 1 presents the primary and secondary objectives for the study expressed using the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials (U.S. Food and Drug Administration [FDA] 2020). Table 2 presents the remaining objectives and corresponding endpoints.

Table 1 Primary and Secondary Objectives and Corresponding Estimands

Primary Objective	Estimand Definition
• To evaluate the efficacy of astegolimab compared with placebo	• Population: individuals with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period – A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) that lead to treatment (duration ≥ 3 days) with systemic corticosteroids (oral, IV, or IM) at a dose of > 10 mg/day prednisolone equivalent and/or antibiotics – A severe COPD exacerbation is defined as new or increased COPD symptoms that lead to hospitalization (duration > 24 hours) or lead to death • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: The event will be classified as a

	"moderate COPD exacerbation" under the composite strategy. Additionally, since participants may continue in the study after the treatment discontinuation, all subsequent measurements after the prohibited medication use will be censored. – Death related to COPD exacerbation: The handling strategy will follow a composite approach since death related to COPD exacerbation is already incorporated into the exacerbation definition as a severe exacerbation and will not be counted twice when calculating the number of exacerbations – Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: The treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy) – Change to initial treatment regimen: The treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy) – Death not related to COPD exacerbation: Data will be censored after the death occurrence (i.e., hypothetical strategy) • Population-level summary: RR for annualized rate of moderate and severe COPD exacerbations

Secondary Objectives	Estimand Definition
• To evaluate the efficacy of astegolimab compared with placebo	• Population: individuals with COPD who are former or current smokers, have a history of frequent exacerbations and have a blood eosinophil level < 300 cells/μL. • Endpoint: annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period. – A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) that lead to treatment (duration≥ 3 days) with systemic corticosteroids (oral, IV, or IM) at a dose of> 10 mg/day prednisolone equivalent and/or antibiotics. – A severe COPD exacerbation is defined as new or increased COPD symptoms that lead to hospitalization (duration> 24 hours) or lead to death. • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: the event will be classified as a "moderate COPD exacerbation" under the composite strategy. Additionally, since participants may continue in the study after the treatment discontinuation, all subsequent measurements after the prohibited medication use will be censored. – Death related to COPD exacerbation: The handling strategy will follow a composite approach since death related to COPD exacerbation is already incorporated into the exacerbation definition as a severe exacerbation and will not be counted twice when calculating the number of exacerbations – Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy). – Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the

	initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy). – Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy). • Population-level summary: RR for annualized rate of moderate and severe COPD exacerbations.
• To evaluate the efficacy of astegolimab compared with placebo	• Population: individuals with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: time to first moderate or severe COPD exacerbation during the 52-week treatment period • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: the event will be classified as a "moderate COPD exacerbation" under the composite strategy. Additionally, since participants may continue in the study after the treatment discontinuation, all subsequent measurements after the prohibited medication use will be censored. – Death related to COPD exacerbation: The handling strategy will follow a composite approach since death related to COPD exacerbation is already incorporated into the exacerbation definition as a severe exacerbation and will not be counted twice when calculating the number of exacerbations – Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment

	discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy). – Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy). – Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy). • Population-level summary: HR for time to first COPD exacerbation
• To evaluate the efficacy of astegolimab compared with placebo	• Population: individuals with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: – Absolute change from baseline in HRQoL at Week 52, as assessed through the SGRQ-C total score – Absolute change from baseline in post-bronchodilator FEV_1 (liters) at Week 52 – Absolute change from baseline in E-RS:COPD total score at Week 52 • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: The event will be handled using a composite strategy consistent with our primary estimand. All measurements at each planned visit following the ICE will be imputed using the 5th

	percentile of the worst outcomes in the placebo arm at each visit. – Death related to COPD exacerbation: the handling strategy will be same as the use of prohibited medications for management of COPD exacerbation risk that lead to treatment discontinuation. – Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy). – Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy). – Death not related to COPD exacerbation: Data will be censored after the death occurrence (i.e., hypothetical strategy). • Population-level summary: difference in mean absolute change at Week 52
• To evaluate the efficacy of astegolimab compared with placebo	• Population: individuals with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: proportion of individuals with improvement in HRQoL, defined as a decrease from baseline of ≥4 points in SGRQ-C total score, at Week 52 • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: under the composite strategy, since participants may continue in the study after the treatment discontinuation, all subsequent measurements after the event will

	be imputed as failure to achieve the improvement, assuming treatment failure for COPD. – Death related to COPD exacerbation: the handling strategy will be same as the use of prohibited medications for management of COPD exacerbation risk that lead to treatment discontinuation. – Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy). – Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy) – Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy). • Population-level summary: odds ratio of having improvement in HRQoL
• To evaluate the efficacy of astegolimab compared with placebo	• Population: individuals with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: annualized rate of severe COPD exacerbations over the 52-week treatment period • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W

	• Intercurrent events and handling strategies: – Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: participants may continue in the study after the treatment discontinuation, all subsequent measurements after event will be censored (hypothetical strategy). – Death related to COPD exacerbation: The handling strategy will follow a composite approach since death related to COPD exacerbation is already incorporated into the exacerbation definition as a severe exacerbation and will not be counted twice when calculating the number of exacerbations – Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy). – Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy). – Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy). • Population-level summary: RR for annualized rate of severe COPD exacerbations

COPD=chronic obstructive pulmonary disease; E-RS:COPD=Evaluating Respiratory Symptoms in COPD; FEV_1=forced expiratory volume in 1 second; HR=hazard ratio; HRQoL=health-related quality of life; IM=intramuscular; IV=intravenous; Q2W=every 2 weeks; Q4W=every 4 weeks; RR=rate ratio; SC=subcutaneous; SGRQ-C=St. George's Respiratory Questionnaire-COPD; SOC=standard of care

Table 2 Other Secondary and Exploratory Objectives and Endpoints

Secondary Objectives	Corresponding Endpoints
• To evaluate the safety of astegolimab compared with placebo	• Incidence and severity of all TEAEs, including SAEs, AESIs, and TEAEs leading to death or discontinuation • TEAEs severity will be determined according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (HHS 2017) (hereafter referred to as the DAIDS Toxicity Grading Scale), with slight modifications for clarity and for alignment with internal practices (see Protocol Appendix 8) • Change from baseline in selected vital signs • Change from baseline in selected clinical laboratory test results and ECGs
• To characterize the astegolimab PK profile	• Serum concentration of astegolimab at specified timepoints
• To evaluate the immune response to astegolimab	• Prevalence of ADAs at baseline and incidence of ADAs during the study
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of astegolimab compared with placebo	• Change in COPD symptoms as measured by the E-RS:COPD total score at Week 24 • Change in E-RS:COPD individual domain scores (breathlessness, cough and sputum, and chest symptoms) from baseline at Week 24 and 52 • Change in EXACT individual domain scores (tired or weak, sleep disturbance, and scared or worried) from baseline at Week 24 and 52 • Proportion of participants with HRQoL improvement, defined as a decrease from baseline of ≥4 points in SGRQ-C total score, at Week 12 and Week 24

Exploratory Objectives	Corresponding Endpoints
	• Proportion of participants with symptom improvement, defined as a decrease of≥2 points from baseline in E-RS:COPD total score, at Week 24 and Week 52 • Absolute change from baseline in post-bronchodilator FEV_1 (liters) at Weeks 12, 24, and 36 • Annual change rate of FEV_1 (liters/year) • Absolute change from baseline in post-bronchodilator FVC (liters) at Weeks 12, 24, 36 and 52 • Annualized rate of moderate COPD exacerbations over the 52-week treatment period • Duration of hospital stay for severe COPD exacerbations • Proportion of severe COPD exacerbations requiring hospital readmission within 30 days • Absolute change from baseline in daily step count at Weeks 12, 24, and 52 • Absolute change from baseline in time in moderate and vigorous physical activity at Weeks 12, 24, and 52 • Overall survival, defined as the time from randomization to death from any cause
• To evaluate potential relationships between drug exposure and the efficacy and safety of astegolimab	• Relationship between serum concentration or PK parameters for astegolimab and efficacy endpoints • Relationship between serum concentration or PK parameters for astegolimab and safety endpoints
• To evaluate potential relationships between selected covariates and exposure to astegolimab	• Relationship between selected covariates and serum concentration or PK parameters for astegolimab
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, PK or biomarker endpoints

Exploratory Objectives	Corresponding Endpoints
• To identify and/or evaluate biomarkers that are predictive of response to astegolimab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of astegolimab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety or pharmacokinetics	• Relationship between biomarkers in blood, plasma, and serum (listed in Protocol Section 8.9) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
• To evaluate health status utility scores of participants treated with astegolimab compared with placebo	• Change from baseline in EuroQol (EQ)-5D-5L index-based and VAS scores at Week 52

ADA=anti-drug antibody; AESI=adverse event of special interest; COPD=chronic obstructive pulmonary disease; DAIDS=Division of AIDS; E-RS:COPD=Evaluating Respiratory Symptoms in COPD; ECG=electro cardio gram; EQ-5D-5L=EuroQoL Five-Dimension-Five Level Questionnaire; EXACT=EXAcerbations of Chronic Pulmonary Disease Tool; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HHS=Health and Human Services; HRQoL=health-related quality of life; PD=pharmacodynamics; PK=pharmacokinetic; SAE=serious adverse event; SGRQ-C=St. George's Respiratory Questionnaire-COPD; TEAE=treatment-emergent adverse event; VAS=Visual Analog Scale.

1.2 STUDY DESIGN

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of astegolimab in combination with standard of care (SOC); (defined in Protocol Section 6.1.1) compared with placebo in combination with SOC, in participants with COPD who are former or current smokers and have a history of frequent exacerbations. Approximately 1290 participants will be enrolled during the global enrollment phase of this study.

Following a screening period of at least 7 days and to up to 4 weeks, participants will be randomized in a 1:1:1 ratio to 1 of 3 treatment arms to receive blinded treatment with either astegolimab or placebo. Randomization will be stratified by smoking status at screening (former smoker vs. current smoker) and region.

The first dose of study drug (astegolimab or placebo) will be administered on Day 1; treatment will continue through Week 50, followed by a 12-week safety follow-up period. The treatment regimens for each arm are as follows:

- Astegolimab 476 mg subcutaneous (SC) every 2 weeks (Q2W)

- Astegolimab 476 mg SC every 4 weeks (Q4W)

  To ensure that all study participants undergo the same visit schedule, participants randomized to the Q4W dosing arm will alternate between injections of astegolimab and placebo Q2W (beginning with astegolimab on Day 1), thus receiving astegolimab Q4W.
- Placebo SC Q2W

Participants will return to the clinic Q2W through the treatment completion visit at Week 52. The primary endpoint analyses will be conducted using the 52-week treatment period data for all participants.

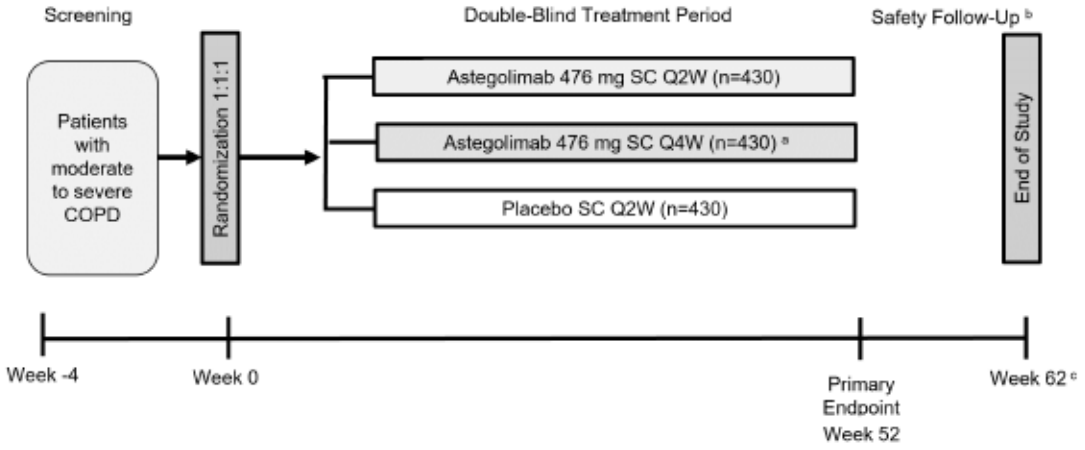
If a separate open-label extension (OLE) study, Study GB43374, will be open and available in their respective country, all participants enrolled in this study and who have completed the Week 52 visit will be given the option to either participate in OLE Study GB43374, if eligible (see Protocol Section 4.1.1), or enter the safety follow-up period (see Protocol Section 4.1.2). If OLE Study GB43374 is not opened, all participants who complete the Week 52 visit, including those participants receiving continued blinded treatment after Week 52, will enter the safety follow-up period. All participants will undergo a safety follow-up visit 12 weeks after their final dose of study drug (regardless of the length of treatment received).

Participants who do not meet the criteria for participation in this study (screen failure) may qualify for 2 re-screening opportunities (for a total of 3 screenings per participant) at the investigator's discretion (see Protocol Section 5.4). The investigator will record reasons for screen failure in the screening log.

After completion of the global enrollment phase, additional participants could be enrolled in an extended China enrollment phase at sites in mainland China, Hong Kong and Taiwan. Similarly, there is an extended Japan enrollment phase at sites in Japan.

A study schema is provided (see Figure 1). A schedule of activities is provided in Protocol Section 1.3 (see Protocol Table 1).

Figure 1 Study Schema



COPD=chronic obstructive pulmonary disease; OLE=open-label extension; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous.

[a] To ensure that all study participants undergo the same visit schedule, participants randomized to the Q4W dosing arm will alternate between injections of astegolimab and placebo Q2W thus receiving astegolimab Q4W.

[b] Participants will enter the safety follow-up period and undergo end of study assessments 12 weeks after their last dose of study drug, as detailed in Protocol Section 4.1.2.

[c] Participants enrolled in this study may have the opportunity to participate in OLE Study GB43374, if eligible, as detailed in Protocol Section 4.1.1.

1.2.1 Treatment Assignment and Blinding

1.2.1.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an interactive voice/web-based response system (IxRS).

Participants will be randomly assigned to 1 of 3 treatment arms: astegolimab 476 mg Q2W, astegolimab 476 mg Q4W, or placebo. Randomization will occur in a 1:1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by smoking status at screening (former smoker vs. current smoker) and region.

The randomization method implemented in the China and Japan extension phase cohorts was the same as that implemented in the global enrollment phase.

1.2.1.2 Blinding

Study site personnel and participants will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to participant treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group

responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and independent Data Monitoring Committee (iDMC) members.

While pharmacokinetic (PK) and immunogenicity samples must be collected from participants assigned to the comparator arm to maintain the blinding of treatment assignment, PK and anti-drug antibody (ADA) assay results for such participants are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participant treatment assignments to identify appropriate samples for analysis. PK samples from participants assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all participants. Postbaseline immunogenicity samples from participants assigned to the comparator arm will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should inform the Medical Monitor that the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per the health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to a drug listed in Protocol Section 8.5.4. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

1.2.2 Independent Review Facility

No Independent Review Facility (IRF) is planned for this study.

1.2.3 Data Monitoring

An iDMC will monitor safety data on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC roles and responsibilities. The iDMC will meet at regular intervals to review unblinded safety data prepared by an external independent Data Coordinating Center (iDCC). In addition, ad hoc reviews may be requested by the iDMC or the Sponsor at any time to address potential safety concerns.

Safety monitoring reviews conducted by the iDMC will include unblinded evaluation of all adverse events, serious adverse events, adverse events of special interest, major protocol deviations, electro cardio grams (ECGs), and relevant laboratory data. The iDMC may recommend stopping the study early for safety reasons; however, the iDMC may not recommend stopping the study early for reasons of positive efficacy.

Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs).

Full details of the roles, responsibilities, membership, scope of activities, meeting schedule, and communication plan will be provided in the iDMC Charter.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The primary comparison of interest for this study is the rate ratio (RR) for the annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period.

The primary efficacy analysis for this study will compare each of the two astegolimab treatment groups with placebo, as follows:

- Astegolimab Q2W compared with placebo
- Astegolimab Q4W compared with placebo

For each of the two comparisons, the null hypothesis (H_0) for the primary endpoint is that the annualized exacerbation rates (AERs) are the same in the treatment and placebo arms (denoted as $AER_{treatment}$ and $AER_{placebo}$), or the RR between AERs is 1. The alternative hypothesis (H_a) is that the AERs are different between treatment and placebo arms, or the RR between AERs is not 1:

- H_0: $AER_{treatment} = AER_{placebo}$, or $RR = 1$, versus
- H_a: $AER_{treatment} \neq AER_{placebo}$, or $RR \neq 1$

The null and alternative hypotheses will be tested at a two-sided 0.05 significance level.

Null and alternative hypotheses of a similar form will be tested for all key secondary efficacy analyses. All hypothesis tests will be two-sided unless stated otherwise.

For the primary efficacy endpoint, annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period in overall population, Type I error will be controlled using a fixed sequence testing procedure at a 5% significance level in the following order:

1. Astegolimab Q2W compared with placebo
2. Astegolimab Q4W compared with placebo

For the secondary efficacy endpoints and the annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period in participants with low baseline blood eosinophil level (< 300 cells/µL) , hypothesis testing will be gated on the success of the primary efficacy endpoint. For each astegolimab dose arm tested to be statistically different from placebo in the primary endpoint, the following secondary efficacy endpoints will be tested within the dose arm, in the order specified below. This testing procedure is intended to manage the Type I error rate among the secondary efficacy endpoints within the dose arm, not across dose arms.

1. Absolute change from baseline in health-related quality of life (HRQoL) at Week 52, as assessed through the St. George's Respiratory Questionnaire-COPD (SGRQ-C) total score in overall population
2. Annualized rate of severe COPD exacerbations over the 52-week treatment period in overall population
3. Time to first moderate or severe COPD exacerbation during the 52-week treatment period in overall population
4. Absolute change from baseline in post-bronchodilator forced expiratory volume in 1 second (FEV_1) (liters) at Week 52 in overall population
5. Absolute change from baseline in E-RS: COPD total score at Week 52 in overall population
6. Proportion of participants with improvement in HRQoL, defined as a decrease from baseline of≥4 points in SGRQ-C total score, at Week 52 in overall population
7. Annualized rate of moderate and severe COPD exacerbations (AER) over the 52-week treatment period in participants with low baseline blood eosinophil level (< 300 cells/µL)

2.2 SAMPLE SIZE DETERMINATION

During the global enrollment phase, a total of approximately 1290 participants will be randomly allocated in a 1:1:1 ratio to receive astegolimab Q2W, astegolimab Q4W, or placebo. The sample size provides approximately 90% power to detect a 20% reduction in annualized COPD exacerbation rate (0.8 RR) between one astegolimab arm and the

placebo arm, assuming a 1.5 AER in the placebo arm, a 15% dropout rate, a two-sided significance level of 0.05, and a Poisson overdispersion parameter of 1.3.

2.2.1 Sample Size for China Population

China subpopulation will include all participants enrolled in mainland China, and Taiwan and Hong Kong.

To ensure a total of approximately 150 participants in the China subpopulation (with approximately 135 participants enrolled in China mainland), this study originally planned an extended China enrollment phase to allow additional Chinese participants after completion of the global enrollment phase. However, due to accelerated enrollment in China population, the last enrollment date during initially planned China extension phase was about 6 weeks after the last enrollment date during original global enrollment phase. To avoid having multiple clinical cutoff dates (i.e. one for global population and one for China subpopulation) within a short period, the sponsor has extended global population by using the China subpopulation cutoff date for the primary analysis. As such, there would be no participants in the originally planned China extension cohort.

2.2.2 Sample size for Japan Population

After completion of the global enrollment phase, additionally Japanese participants will be enrolled in an extended Japan enrollment phase to ensure a total of approximately [redacted] participants in the Japan subpopulation. The Japan subpopulation includes all participants enrolled at sites in Japan (during both the global enrollment phase and the extended Japan enrollment phase).

3. ANALYSIS SETS

The analysis data sets for the purposes of analysis are presented in Table 3.

Table 3 Analysis Data Sets

Analysis Data Sets	Description
ITT	• All randomized participants, regardless of whether or not the participant received the assigned treatment • Participants will be grouped according to the treatment assigned at randomization by the IxRS
mITT	• All randomized participants who received at least 1 dose of study drug • Participants will be grouped according to the treatment assigned at randomization by the IxRS

Analysis Data Sets	Description
Safety evaluable	• All randomized participants who received at least 1 dose of study drug • Participants will be analyzed based on the treatment they actually received (which may be different from the treatment to which the participant was randomized)
Pharmacokinetic evaluable	• All randomized participants who received at least 1 dose of study drug and had at least one postdose PK assessment
Immunogenicity evaluable	• All randomized participants with at least one postdose ADA assessment

ADA=anti-drug antibody; ITT=intent-to-treat; IxRS=interactive voice or web-based response system; mITT=modified intent-to-treat; PK=pharmacokinetic.

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

The primary analyses will be performed when all participants enrolled globally, excluding the China and Japan extension cohorts (see Section 2.2.1 and Section 2.2.2 respectively), have completed or discontinued from the 52-week double blind treatment period. This extended global analysis population is hereafter referred to as global population or primary analysis population, interchangeably. Clinical study reports (CSR) based on the primary analyses of these cohorts may be prepared for the purpose of regulatory filings.

Participant disposition will be summarized based on the ITT population, based on treatment assigned at randomization.

Efficacy analyses will be conducted on the modified intent-to-treat (mITT) population, consisting of all participants randomized in the study who received at least one dose of study drug, with participants grouped according to the treatment assigned at randomization.

In efficacy analyses, comparison will be performed between each of the two treatment groups and the placebo group as follows:

- Astegolimab Q2W compared with placebo
- Astegolimab Q4W compared with placebo

Hypothesis testing and estimation of treatment effects will be performed with regression models fit using data from all three treatment arms and with indicator variables to characterize the treatment comparison described above. Multiplicity adjustment will be performed as described in Section 2.1. Unless otherwise noted, the covariates adjusted in the efficacy analyses and the grouping in the subgroup analyses will be based on the

stratification factors smoking status at screening (former smoker vs. current smoker) directly from IxRS and region derived based on the country a study site is located in.

All safety analyses will be performed in the safety evaluable set, unless otherwise specified. Participants will be analyzed according to the treatment they actually received.

Analyses of demographics and baseline characteristics will be based on the mITT population, based on treatment assigned at randomization.

Baseline value of any variable is defined as the last available data point prior to or on the same date of the first administration of study drug unless otherwise specified.

4.2 PRIMARY ENDPOINT ANALYSIS

4.2.1 Definition of Primary Endpoint

The primary endpoint is annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period, as defined in Table 1.

4.2.1.1 Primary Estimand

The primary estimand is defined in Table 1.

Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation will be treated with a composite strategy, which will produce a conservative estimate of treatment effect by assuming treatment failure in such instances. This approach aims to differentiate the efficacy of the investigational treatment from the effects of unmanaged exacerbations, ensuring the robustness of our conclusions.

Handling strategies of the other types of intercurrent events are chosen in order to maintain the ITT principle and thus mirror typical clinical practice and maintain the generalizability of the trial results.

All missing data, including missing data due to deaths, will be considered similar to data from other participants in the same treatment group with the same baseline characteristics with no such missing data (compatible with missing at random [MAR] assumption). A tipping point analysis in Section 4.2.3 will be performed to assess the robustness of conclusion assuming data missing not at random.

4.2.1.2 Secondary Estimand

The secondary estimand of the primary endpoint is defined in Table 1. This secondary estimand is defined identically to the primary estimand, with the exception of the population. For the purpose of analysis, each participant's baseline value of blood eosinophil level will be used to determine if they have < 300 cells/µL. A testing hierarchy will be used to control the overall Type I error rate at 5%, as described in Section 2.1.

4.2.2 Main Analytical Approach for Primary Endpoint

The unadjusted AER will be estimated as the total number of COPD exacerbations observed over the treatment period divided by the total participant-years at risk. For each individual participant, years at risk will be derived as the number of days from the date of the first administration of study drug to the date of completion or discontinuation of study in the double-blind treatment period, divided by 365.25 days.

The adjusted AER will be estimated using a Negative Binomial regression model. The model will include the total number of events observed over the 52-week treatment period as the response variable, with the treatment group, the stratification factors as specified in Section 4.1 and number of moderate or severe COPD exacerbations within 12 months prior to screening as covariates. The natural log transformation of the participant's time at risk, as defined above, will be used as an offset term in the model.

For each of the astegolimab treatment arms compared with placebo, the RR for annualized rate of moderate and severe COPD exacerbations will be estimated using the same model describe above, along with the associated 95% confidence intervals (CIs) and p-values. The absolute and relative differences in AERs, expressed as events per year and rate reduction, respectively, will also be provided.

4.2.3 Sensitivity Analysis

Sensitivity analysis using Poisson regression model

The primary efficacy endpoint will be analyzed using a Poisson regression model as a sensitivity analysis. The same model (i.e., one adjusted for the same covariates as described in Section 4.2.2) will be used.

Sensitivity analysis with number of COPD exacerbation within 12 months prior to screening removed from the model using negative binomial and Poisson regression model respectively

A sensitivity analysis will be performed with adjustment variable number of COPD exacerbation within 12 months prior to screening removed from the model. All other elements of the analysis will remain the same as in the primary analysis. In addition, a Poisson regression model will be used with the same model specification.

Sensitivity analysis using negative binomial and Poisson regression model respectively using baseline FEV_1 as an additional adjustment variable

A different model additionally adjusted for baseline FEV_1 (i.e., one adjusted for baseline FEV_1 and the covariates described in Section 4.1), will also be used for the Negative Binomial and Poisson regression model, respectively. All other elements of the analysis will remain the same as in the primary analysis.

Sensitivity analysis using negative binomial and Poisson regression model respectively using baseline SGRQ-C total score as an additional adjustment variable

A sensitivity analysis will be performed with adjustment variable of baseline SGRQ-C total score. The analysis will be conducted in a similar manner to the sensitivity analysis using baseline FEV_1 as an additional adjustment variable as mentioned above.

Sensitivity analysis using region stratification factor from IxRS

In the main analysis specified in Section 4.2.2, for model adjustment, region will be allocated based on the country a study site is located in. A sensitivity analysis will be performed using region as per the manual data entry in IxRS by the study sites. All other elements of the analysis will remain the same as in the primary analysis.

Tipping point analysis

For the primary endpoint, tipping point analysis via multiple imputation of event counts assuming a range of deltas will be performed. Event counts will be imputed at the participant level for the observed period between the last study visit and Week 52 visit for participants who discontinued from the study early. An event count for each unobserved period will be imputed by first fitting a negative binomial regression model to the observed data and sampling from the posterior distribution of the model parameter estimates. These sampled parameter estimates along with the participant-specific observed covariate values, observed exacerbation counts, and length of unobserved interval will be used in conjunction with a random number generator to impute an event count for the unobserved time period, which is added to the observed event count (Keene et al. 2014). These augmented datasets will be analyzed according to the main analysis method (Section 4.2.2) and the results combined using Rubin's rules.

In the tipping point analysis, a range of delta values will be used to adjust the underlying event rate used for imputation in the astegolimab and placebo arms independently based on a grid of delta adjustment. The delta values will be chosen based on the treatment effect (RR) observed for a given astegolimab arm compared with placebo from the primary analysis (Section 4.2.2). The range of delta values will include cases where dropouts from the astegolimab arm are assumed to have worse outcomes than dropouts from the placebo arm. The resulting point estimates of treatment effect and corresponding p-values under each delta value for each astegolimab and placebo comparison will be tabulated. Additional sensitivity analyses may be considered as appropriate.

4.2.4 Supplementary Analyses

4.2.4.1 Analysis excluding participants from sites with confirmed serious good clinical practice (GCP) non-compliance

Sites with confirmed serious GCP non-compliance raise concerns on data integrity. To assess the impact of data issues from these sites, the primary analysis of the primary

endpoint will be repeated with participants from these sites excluded from the mITT population.

4.2.4.2 Handling of deaths not related to COPD using composite strategy

The primary estimand handles deaths that are not related to COPD using a hypothetical strategy, estimating the treatment effect as if these deaths hadn't occurred. For a more conservative estimation of the treatment effect, the primary analysis of the primary endpoint will be repeated, treating non-COPD deaths as severe COPD exacerbations in the primary endpoint, while keeping all other elements of the analysis remaining the same as in the primary analysis.

4.2.4.3 Subgroup Analyses for Primary Endpoint

The generalizability of the primary endpoint results when comparing astegolimab to placebo will be investigated by estimating the treatment effect in subgroups based on stratification factors, key baseline demographics, disease characteristics, and biomarkers, as listed below.

- Age (40 to < 65 years, ≥ 65 years)
- Sex (male, female)
- Race (White, Black or African American, Asian, Other)
- Ethnicity (Hispanic, Not Hispanic)
- Region (North America, Latin America, Central/Eastern European Union [EU], Western EU/Rest of the world [ROW])
- Baseline smoking status (former smoker, current smoker)
- Baseline blood eosinophil level (≥ 300 cells/µL, < 300 cells/µL)
- Baseline blood eosinophil level (≥ 150 cells/µL, < 150 cells/µL)
- Baseline blood eosinophil level (≥ 300 cells/µL, ≥ 150 cells/µL to < 300 cells/µL, < 150 cells/µL)
- Number of COPD exacerbation within the last 12 months period (2, > 2)
- Hospitalization for COPD within the last 12 months prior to screening (yes, no)
- Baseline COPD triple therapy (yes, no)
- Baseline inhaled corticosteroid (ICS) (yes, no)
- Baseline azithromycin (yes, no)
- Baseline roflumilast (yes, no)
- Baseline diagnosis of chronic bronchitis (yes, no)
- Baseline Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage (Moderate: FEV_1 ≥ 50 % predicted to < 80 % predicted; Severe: FEV_1 ≥ 30 % predicted to < 50 % predicted; Very severe: FEV_1 < 30 % predicted)

Additional subgroups may be considered as appropriate.

Summaries of primary endpoint by these subgroups will be provided in forest plots, including AERs and estimates for rate ratio and their 95% CIs from negative binomial regression adjusted based on the stratification factors as specified in Section 4.1. For the subgroup analyses by stratification factor, the corresponding stratification factor will be removed when running that particular subgroup analysis. For example, when analysis for participants who are current smokers is performed, smoker status (former vs current) will be removed as a covariate in the model. Some subgroup analyses may have limited sample sizes, potentially causing convergence issues in the statistical models. Those subgroup results may be summarized descriptively only.

4.3 SECONDARY ENDPOINTS ANALYSES

Estimand definitions of the secondary efficacy endpoints are located in Table 1 in Section 1.1 and will not be repeated in this section. This section will focus on further details about the analyses.

A testing hierarchy will be used to control the overall Type I error rate at 5%, as described in Section 2.1

4.3.1 Key/Confirmatory Secondary Endpoints

4.3.1.1 Time to first moderate or severe COPD exacerbation

Time to first moderate or severe COPD exacerbation is defined as the time from the first administration of study drug to the first incidence of moderate or severe COPD exacerbation event during the 52-week treatment period. Participants who have not had an event will be censored at the end of their time at risk as defined in Section 4.2.2. Participants who are randomized without any post-baseline information will be censored at the date of randomization plus 1 day.

The stratified log-rank test will be used to compare the time to first moderate or severe COPD exacerbations between astegolimab and placebo, adjusting for the stratification factors specified in Section 4.1. The unstratified log-rank test will be used as a sensitivity analysis. If, at the time of analysis, the smallest stratum per arm is less than 5 participants, unstratified analyses will be used as the primary analysis.

The hazard ratio (HR) for time to first moderate or severe COPD exacerbation will be estimated by a Cox proportional hazards regression model, adjusted for the stratification factors specified in Section 4.1. Point estimates, their 95% confidence interval (CI) and associated p-values for the treatment effect will be calculated based on the model.

4.3.1.2 Absolute change from baseline in SGRQ-C total score at Week 52

The SGRQ-C is a self-report questionnaire designed to measure the impact of COPD on health and well-being through the participant's perception of COPD-related experiences (Meguro et al. 2007). It has 40 items and three sub-domains: symptoms, activity, and impacts. Each item response has a unique, empirically derived weight ranging from 0 to

100. Scores are calculated as the proportion of the sum of positive item weights over the total possible sum weight as described in Appendix 1.

The absolute change in SGRQ-C total score from baseline will be summarized by treatment arm and timepoint. The difference in mean absolute change from baseline in SGRQ-C total score at Week 52 from baseline between each astegolimab treatment arm and placebo will be estimated using a mixed model for repeated measures (MMRM). The model will use the absolute change from baseline as the response variable and include terms for treatment arm, study visit, treatment arm by study visit interaction, baseline value (as a continuous variable) as well as its interaction with study visit, and the stratification factors specified in Section 4.1. Study visit will be included as a categorical variable. An unstructured covariance matrix will be specified to model the within-subject errors. If the analysis fails to converge, the following covariance structures will be tested: compound symmetry, first-order autoregressive (AR[1]), and Toeplitz. The covariance structure converging to the best fit, based on Akaike's information criterion (AIC), will be used. Point estimates, 95% CIs, and p-values for the treatment effect (astegolimab versus placebo) will be calculated for all study visits, including Week 52.

4.3.1.3 Absolute change from baseline in post-bronchodilator FEV_1 at Week 52

Post-bronchodilator FEV_1 is defined as the FEV_1 value taken in the spirometry after the procedure for bronchodilator testing.

This key secondary endpoint will be analyzed in a similar manner as the SGRQ-C total score (see Section 4.3.1.2) to estimate the absolute change and difference in mean absolute change in FEV_1.

4.3.1.4 Absolute change from baseline in Evaluating Respiratory Symptoms in COPD (E-RS:COPD) total score at Week 52

The EXAcerbations of Chronic Pulmonary Disease Tool (EXACT) is administered as an eDiary that assesses COPD exacerbations (Leidy et al. 2010). The 14-item questionnaire contains 4 domains: breathlessness (5 items), cough and sputum (3 items), chest symptoms (3 items), and additional attributes (tired or weak, sleep disturbance, and scared or worried (3 items). The EXACT has a recall period of "today."

The subset E-RS:COPD is composed of the breathlessness, cough and sputum, and chest symptoms domains of the EXACT (11 total items) and, as such, it specifically assesses COPD symptoms (Leidy et al. 2014). An E-RS:COPD total score is derived based on the 3 domains. Each item response will be converted to an item-level raw score. The daily E-RS COPD total score is calculated by summing across the 11 item-level scores, as described in Appendix 2.

The baseline weekly E-RS: COPD total score is calculated as the average of daily total score over 7 days prior to the date of first study drug administration. The weekly E-RS COPD total score post-baseline is calculated as the average of daily total score over 7 days prior to the date of visit under analysis (Leidy et al. 2014). For both baseline and post-baseline weekly E-RS: COPD total score, daily scores need to be present for a minimum of 4 out of the 7 days. If fewer than 4 days of data are available, the weekly E-RS: COPD total score will be recorded as missing. No imputation will be done for the daily EXACT Respiratory Symptoms (E-RS) score.

This key secondary endpoint will be analyzed in a similar manner as the SGRQ-C total score (see Section 4.3.1.2) to estimate the absolute change and difference in mean absolute change in E-RS: COPD total score.

4.3.1.5 Proportion of participants with SGRQ-C improvement at Week 52

The proportion of participants with SGRQ-C improvement is defined as the proportion of participants with an absolute change from baseline in SGRQ-C total score ≤ -4 points, i.e., a decrease from baseline of ≥ 4 points (Jones 2005). The SGRQ-C total score is calculated as described in Section 4.3.1.2.

For participants without Week 52 data, their last available assessment of SGRQ-C will be used. Participants without post-baseline assessments will be excluded from the analysis.

The proportion of participants with SGRQ-C improvement will be summarized by treatment arm and timepoint. The odds ratio of having SGRQ-C improvement will be estimated using a logistic regression model. The model will include terms for treatment arm, baseline SGRQ-C total score, and the stratification factors specified in Section 4.1. Point estimates, 95% CIs, and p-values for the treatment effect (astegolimab versus placebo) will be calculated.

4.3.1.6 Annualized rate of severe COPD exacerbations

A severe COPD exacerbation is defined as new or increased COPD symptoms that lead to hospitalization (duration $>$ 24 hours) or lead to death.

This key secondary endpoint will be analyzed in a similar manner as the primary endpoint (see Section 4.2.2), except that the number of severe COPD exacerbations within 12 months prior to screening will be used as one of the adjustment covariates in place of the number of moderate or severe COPD exacerbations within 12 months prior to screening to be consistent with the definition of this endpoint, to estimate AERs for each treatment arm, as well as the RRs between astegolimab and placebo and their 95% CI. The use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation will not be classified as a "severe COPD

exacerbation" using the composite strategy since it is already considered as a "moderate COPD exacerbation" in the primary estimand.

4.3.1.7 Subgroup analyses

Subgroup analyses will also be performed for all key secondary endpoints based on subgroups defined in Section 4.2.4.3. Summaries by these subgroups will be provided in forest plots, including point estimates and their 95% CIs using the corresponding estimand associated with endpoints. For the subgroup analyses by stratification factor, the corresponding stratification factor will be removed when running that particular subgroup analysis. For example, when analysis for participants who are current smokers is performed, smoker status (former vs current) will be removed as a covariate in the model.

4.4 EXPLORATORY ENDPOINTS ANALYSIS

Change in COPD symptoms as measured by the E-RS:COPD total score at Week 24

This exploratory endpoint is defined as the absolute change from baseline in E-RS:COPD total score at Week 24. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C total score at Week 52 (see Section 4.3.1.2).

Change in E-RS:COPD individual domain scores (breathlessness, cough and sputum, and chest symptoms) from baseline at Week 24 and 52

This exploratory endpoint is defined as the absolute change in E-RS:COPD individual domain scores (breathlessness, cough and sputum, and chest symptoms) from baseline at Week 24 and 52. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C total score at Week 52 (see Section 4.3.1.2).

Change in EXACT individual domain scores (tired or weak, sleep disturbance, and scared or worried) from baseline at Week 24 and 52

This exploratory endpoint is defined as the absolute change in EXACT individual domain scores (tired or weak, sleep disturbance, and scared or worried) from baseline at Week 24 and 52. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C total score at Week 52 (see Section 4.3.1.2).

Proportion of participants with HRQoL improvement, defined as a decrease from baseline of ≥ 4 points in SGRQ-C total score, at Week 12 and Week 24

This endpoint is defined as the proportion of participants who had a decrease from baseline of ≥ 4 points in SGRQ-C total score, at Week 12 and Week 24. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of proportion of participants with SGRQ-C improvement at Week 52 (see Section 4.3.1.5).

Proportion of Participants with E-RS: COPD improvement at Week 24 and Week 52

The proportion of participants E-RS:COPD improvement is defined as the proportion of participants with an absolute change from baseline in E-RS:COPD total score ≤ -2 points, i.e., a decrease from baseline of ≥ 2 points (Leidy et al. 2014). This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of proportion of participants with SGRQ-C improvement at Week 52 (see Section 4.3.1.5).

Absolute Change in Post-bronchodilator FEV_1 at Weeks 12, 24, and 36

This exploratory endpoint is defined as the secondary endpoint of absolute change from baseline in post-bronchodilator FEV_1 at Week 52 (see Section 4.3.1.3). It will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C total score at Week 52 (see Section 4.3.1.2).

Annual change rate of FEV_1 (liters/year)

This exploratory endpoint is defined as FEV_1 change per year. It will be analyzed using a Random Coefficient Regression Model (RCRM). The RCRM will include FEV_1 as the dependent variable (including baseline), treatment group, time from baseline as a continuous variable), and treatment-by-time interaction and the stratification factors specified in Section 4.1 as fixed effects. Participant level random effects will be assumed for the intercept and slope (i.e., time) with a two-dimensional unstructured covariance and errors within each subject independently and identically distributed. Point estimates, 95% CIs and associated p-values will be calculated based on the model.

Absolute Change in Post-bronchodilator forced vital capacity (FVC) at Weeks 12, 24, 36 and 52

This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in (SGRQ-C total score at Week 52 (see Section 4.3.1.2).

Annualized Rate of Moderate COPD Exacerbation

A moderate COPD exacerbation is defined as defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) that lead to treatment (duration ≥ 3 days) with systemic corticosteroids (oral, intravenous [IV], or intramuscular [IM]) at a dose of > 10 mg/day prednisolone equivalent and/or antibiotics. This exploratory endpoint will be analyzed in a similar manner as the primary endpoint (see Section 4.2.2), except that the number of moderate COPD exacerbations within 12 months prior to screening will be used as one of the adjustment covariates in place of the number of moderate or severe COPD exacerbations within 12 months prior to screening to be consistent with the definition of this endpoint.

Duration of Hospital Stay for Severe COPD Exacerbation

For each severe COPD exacerbation event, the duration of hospital stay (days) is defined as the hospital discharge date minus the hospital admission date plus 1. For

participants with multiple severe COPD exacerbation, the duration of hospital stay will be summed. The total duration of hospital stay will be summarized by treatment arm descriptively.

Proportion of Severe COPD Exacerbations Requiring Hospital Readmission within 30 days

For each severe COPD exacerbation event, the hospital discharge date will be compared with the participant's subsequent COPD exacerbation related hospital admission date, if there is one. If the subsequent COPD exacerbation related hospital admission date is within 30 days of the previous discharge day, it is considered as a hospital readmission associated with the severe COPD exacerbation. The proportion is defined as the number of readmissions divided by the number of severe COPD exacerbations. The proportion will be summarized by treatment arm descriptively.

Absolute Change in Daily Step Count at Weeks 12, 24, and 52

The daily step count will be recorded by a physical activity monitor. Weekly step count will be calculated as the average of daily step count over 7 days prior to the visit under analysis. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C) total score at Week 52 (see Section 4.3.1.2).

Absolute Change in Time in Moderate and Vigorous Physical Activity at Weeks 12, 24, and 52

The daily time (minutes) in moderate and vigorous physical activity (MVPA) will be recorded by a physical activity monitor. The weekly time (minute per day) will be calculated as the average daily time in MVPA over 7 days prior to the visit under analysis. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C total score at Week 52 (see Section 4.3.1.2).

Overall survival, defined as the time from randomization to death from any cause during the participant's study participation (i.e., deaths occurring after the safety follow-up or after the participant rolls over to the OLE study will not be included)

This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of time to first moderate or severe COPD exacerbation (see Section 4.3.1.1).

Change from baseline in EuroQol EQ-5D-5L index-based and Visual Analog Scale (VAS) scores at Week 52

To evaluate health status utility scores of participants treated with astegolimab compared with placebo, absolute change from baseline in EuroQol EQ-5D-5L index based score and VAS score will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ at Week 52 (see Section 4.3.1.2).

4.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized participants who received at least 1 dose of study drug, with participants grouped according to treatment received. Safety summaries will include cumulative data until the end of study, with safety follow-up period included for applicable participants.

Safety will be assessed through summaries of exposure to study treatment, treatment-emergent adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Relevant laboratory, vital sign, and ECGs will be summarized by appropriate descriptive statistics by treatment groups with shift tables from baseline, with grades identified as appropriate.

4.5.1 Extent of Exposure

Study treatment exposure, such as treatment duration, and number of doses will be summarized for each treatment arm with descriptive statistics. Reasons for study treatment discontinuation will also be summarized.

4.5.2 Adverse Events

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to the Division of AIDS Table v2.1 (see Protocol Appendix 8). A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest (Protocol Section 8.5.8), adverse events leading to discontinuation from study treatment, and adverse events leading to discontinuation from study will be summarized by mapped terms, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized. Summaries of confirmed or suspected Coronavirus Disease 2019 (COVID-19) AEs and AEs associated with COVID-19 will also be provided. Summary measures include counts and percentages of participants with the adverse event under analysis. Summaries will be performed by treatment arm.

The within-arm cumulative incidence and the difference in cumulative incidence between arms, along with the 95% CIs, will be summarized in a forest plot for the following safety outcomes: all adverse events, all serious adverse events, all adverse events leading to treatment discontinuation, all adverse events determined to be related to study drug, deaths, AESIs, the most common adverse events (by preferred term).

Adverse events may also be summarized by selected subgroups, such as age (40 to<65 years,≥65 years), gender (male, female), race (white, black or African American, Asian, other), baseline smoking status (yes, no) and cardiac disease (yes, no).

In addition, the within-arm AE rate, adjusted for person-years at risk, along with the 95% CIs, will be summarized for all adverse events, serious adverse events, AESIs, and deaths. Total person-years at risk is calculated as the sum of the time intervals (in years) from the start of study treatment to the end of the adverse event reporting period across all patients.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

The number of participants who enroll, discontinue, or complete the study will be summarized by treatment group. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. The impact of COVID-19 will be assessed by including major protocol deviations related to COVID-19.

4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics (including, but not limited to, age, sex, smoking status) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

4.6.3 Pharmacokinetic Analyses

All subjects who received the study drug and who have at least one measurable drug concentration post-dosing will be included in the PK analysis population.

Listings of serum astegolimab concentration by subject and treatment with nominal times, as well as actual sampling times will be provided. Mean serum astegolimab concentration will be tabulated and summarized using descriptive statistics (including population size [N], mean, standard deviation [SD], coefficient of variation [CV]%, median, minimum, maximum, geometric mean, and geometric mean CV%) for each treatment. The concentration data will also be summarized and plotted by ADA-negative and ADA-positive status, as appropriate, to assess the potential impact of immunogenicity on astegolimab exposure. Figures illustrating the time course of mean serum astegolimab concentration for each treatment will be overlaid and presented for relevant comparisons on linear and semi-logarithmic scales, as appropriate.

PK data from this study may be used in population PK analysis in combination of PK data from other studies. A separate analysis plan will be prepared, and the population PK analysis will be presented in a separate report.

Additional PK or exposure-response analyses or exposure-safety analyses may be conducted as appropriate.

The PK-pharmacodynamic (PD) relationship may be explored as appropriate.

4.6.4 Immunogenicity Analyses

The immunogenicity analysis population will consist of all participants with at least one postdose ADA assessment. Participants will be grouped according to treatment

received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The number and proportion of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, participants are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of 1 or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Participants are considered to be ADA-negative if they are ADA-negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA-positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

4.6.5 Biomarker Analyses

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

The biomarker analysis population will be mITT and participants will be grouped according to the treatment assigned at randomization by the IxRS.

Potential predictive biomarkers of astegolimab response will be assessed in primary and key secondary endpoints (e.g., exacerbation rate, time to first exacerbation, FEV_1) to assess if a subset of participants derives enhanced clinical benefit from astegolimab. Predictive biomarker candidates include, but are not limited to, blood eosinophils, serum soluble ST2 (sST2) and germline mutations in IL1RL1.

PD biomarkers (e.g., sST2 and eosinophils) will be assessed to determine pharmacological activity and mechanism of action of astegolimab in participants with COPD. Data will be summarized by absolute levels of the biomarker, as well as absolute and relative changes from levels at Day 1 for each treatment group. Additional PD analyses will be conducted as appropriate.

4.6.6 Analysis of China Subpopulation

Separate analyses will be performed for China subpopulation, where data from all participants enrolled in mainland China, Hong Kong, or Taiwan will be summarized. Results from the China subpopulation analyses will be summarized in a separate Clinical Study Report.

Data for the China subpopulation will be analyzed using the same statistical methods as described in Section 4.1–Section 4.5 when data allow. No formal statistical testing of the

comparison between astegolimab and placebo is planned for the China subpopulation and the clinical data will be descriptively summarized. The China subpopulation results will be interpreted in the context of results from the global population. Thus, the consideration of whether the China subpopulation data is consistent with the results from the global population will be based on the totality of the data, including the direction of efficacy and safety profiles.

4.6.7 Analysis of Japan Subpopulation

Separate analyses will be performed for Japan subpopulation, where data from all participants enrolled in Japan (i.e., during both the global enrollment phase and Japan extension phase) will be summarized.

Data for the Japan subpopulation will be analyzed using the same statistical methods as described in Section 4.1–Section 4.5 when data allow. No formal statistical testing of the comparison between astegolimab and placebo is planned for Japan subpopulation and the clinical data will be descriptively summarized. The Japan subpopulation results will be interpreted in the context of results from the global population. Thus, the consideration of whether the Japan subpopulation data is consistent with the results from the global population will be based on the totality of the data, including the direction of efficacy and safety profiles.

4.6.8 Analysis of East Asian Subpopulation

To support Japan filing, separate analyses may be performed for East Asian subpopulation, where data from all participants enrolled in Japan, mainland China, Hong Kong, Vietnam, Philippines, Republic of Korea, Taiwan and Thailand (i.e., during both the global enrollment phase and China/Japan extension phase) will be analyzed as described in Section 4.6.7.

4.7 INTERIM ANALYSES

No interim analysis is planned.

4.8 CHANGES TO PROTOCOL-PLANNED ANALYSIS

This SAP document clarified the primary analysis population and the trigger of primary analyses, which is currently planned based on the last patient in for originally planned China extension phase (Section 4.1) as the primary analysis population was extended to include the originally planned China extension cohort (Section 2.2.1) to avoid having multiple clinical cutoff dates within short period.

This SAP document clarified the baseline variables to include as adjustment covariates in the main analysis model for primary endpoint (Section 4.2.2). A sensitivity analysis is accordingly planned (Section 4.2.3).

5. SUPPORTING DOCUMENTATION

Refer to:

- **Appendix 1**: Scoring of the St. George's Respiratory Questionnaire For COPD Patients (SGRQ-C)
- **Appendix 2**: Scoring of the EXACT-Respiratory Symptoms (E-RS) Scale

Appendix 1 Scoring of the St George's Respiratory Questionnaire For COPD Patients (SGRQ-C)

The scoring is based on the SGRQ-C manual version No.1.4. A total and three component scores are calculated: Symptoms; Activity; Impacts. Each component of the questionnaire is scored separately:

CALCULATION OF THE SCORE

The score for each component is calculated separately by dividing the summed weights by the maximum possible weight for that component and expressing the result as a percentage:

$$Score = 100 \times \frac{Summed\ weights\ from\ all\ positive\ items\ in\ that\ component}{Sum\ of\ weights\ for\ all\ items\ in\ that\ component}$$

The Symptom component is calculated by summing the weights for all the questions in Part 1, i.e., Questions 1-7. A single response is required to each item. If multiple responses are given to an item, the weights for the multiple positive responses should be averaged then added to the sum.

The Activity component is calculated from the summed weights for the positive responses to items Questions 9 and 12 in Part 2 of the questionnaire.

The Impact component is calculated from Questions 8, 10, 11, 13, 14 in Part 2 of the questionnaire. The weights for all positive responses to items in Questions 10, 11, 13 are summed together with the responses to the single item that should have been checked (ticked) in Questions 8 and 14. In the case of multiple responses to either of these items, the average weight for the item should be calculated.

The Total score is calculated by summing the weights to all the positive responses in each component and the score for each component can be calculated similarly:

$$Score = 100 \times \frac{Summed\ weights\ from\ all\ positive\ items\ in\ the\ questionnaire}{Sum\ of\ weights\ for\ all\ items\ in\ the\ questionnaire}$$

Sum of maximum possible weights for each component and Total:

Symptoms	566.2
Activity	982.9
Impacts	1652.8
Total (sum of maximum for all three components)	3201.9

(Note: these are the maximum possible weights that could be obtained for the worst possible state of the patient).

HANDLING MISSING ITEMS

The Total score can be calculated in the presence of missing data, but only if the domains meet their 'missing items' rules below. If one domain exceeds its permitted number of missed items, then a total score cannot be calculated.

Symptoms (Questions 1-7)

The Symptoms component will tolerate a maximum of 1 missed item. The weight for the missed item is subtracted from the total possible weight for the Symptoms component (566.2) and from the Total weight (3201.9).

Activity (Questions 9 and 12)

The Activity component will tolerate a maximum of 3 missed items. The weight for the missed item is subtracted from the total possible weight for the Activity component (982.9) and from the Total weight (3201.9).

Impacts (Questions 8, 10, 11, 13, 14)

The Impacts component will tolerate a maximum of 5 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts component (1652.8) and from the Total weight (3201.9).

If there are two responses have been given to one question, add the weights of the two checked responses and divide by two. If more than three responses are checked, treat the item as missing.

ITEM WEIGHTS

The following wording of the item is abbreviated and may not correspond exactly with what's used in the questionnaire.

PART 1

Question 1: I cough:

Most days	80.6
Several days	46.3
With chest infections	28.1
Not at all	0.0

Question 2: I bring up phlegm (sputum):

Most days	76.8
Several days	47.0
With chest infections	30.2
Not at all	0.0

Question 3: I have shortness of breath:

Most days	87.2
Several days	50.3
Not at all	0.0

Question 4: I have attacks of wheezing:

Most days	86.2
Several days	71.0
A few days	45.6
With chest infection	36.4
Not at all	0.0

Question 5: How many attacks of chest trouble have you had

3 or more	80.1
1 or 2 attacks	52.3
None	0.0

Question 6: How often do you have good days (with little chest trouble)?

None	93.3
A few	76.6
Most are good	38.5
Every day	0.0

Question 7: If you have a wheeze, is it worse in the morning?

No	0.0
Yes	62.0

PART 2

Question 8: How would you describe your chest condition?

The most important problem I have	82.9
Causes me a few problems	34.6
Causes no problem	0.0

Question 9: Questions about what activities usually make you feel breathless.

Getting washed or dressed	82.8
Walking around the home	80.2
Walking outside on the level	81.4
Walking up a flight of stairs	76.1
Walking up hills	75.1

Question 10: More questions about your cough and breathlessness.

My cough hurts	81.1
My cough makes me tired	79.1
I get breathless when I talk	84.5
I get breathless when I bend over	76.8
My cough or breathing disturbs my sleep	87.9
I get exhausted easily	84.0

Question 11: Questions about other effects your chest trouble may have on you.

My cough or breathing is embarrassing in public	74.1
My chest trouble is a nuisance to my family, friends or neighbours	79.1
I get afraid or panic when I cannot get my breath	87.7
I feel that I am not in control of my chest problem	90.1
I have become frail or an invalid because of my chest	89.9
Exercise is not safe for me	75.7
Everything seems too much of an effort	84.5

Question 12: Questions about how activities may be affected by your breathing.

I take a long time to get washed or dressed	74.2
I cannot take a bath or shower, or I take a long time	81.0
I walk more slowly than other people, or I stop for rests	71.7
Jobs such as housework take a long time, or I have to stop for rests	70.6
If I walk up one flight of stairs, I have to go slowly or stop	71.6
If I hurry or walk fast, I have to stop or slow down	72.3
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf	74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	71.4

Question 13: We would like to know how your chest trouble usually affects your daily life.

I cannot play sports or games	64.8
I cannot go out for entertainment or recreation	79.8
I cannot go out of the house to do the shopping	81.0
I cannot do housework	79.1
I cannot move far from my bed or chair	94.0

Question 14: Tick the statement which you think best describes how your chest affects you.

It does not stop me doing anything I would like to do	0.0
It stops me doing one or two things I would like to do	42.0
It stops me doing most of the things I would like to do	84.2
It stops me doing everything I would like to do	96.7

Appendix 2 Scoring of the EXACT-Respiratory Symptoms (E-RS) scale

ITEM-LEVEL SCORES

Each original item response will be converted to an item-level raw score, by matching the response to the Raw Score Assignment below. The recommended programming for the electronic diary does not allow a study participant to skip individual items. Thus, no missing data are expected for individual item in the electronic data capture setting.

CALCULATION OF THE DAILY SCORE

A daily EXACT (EXAcerbations of Chronic Pulmonary Disease Tool) Respiratory Symptoms (E-RS) Total score is derived by summing across the 11-item level scores converted as above. The Total scores range from 0 to 40.

For each E-RS subscale, sum the item-level scores across the items comprising the subscale, as follow:

RS-Breathlessness: Sum score of item 7, 8, 9, 10, 11 (score range 0-17)
RS-Cough & Sputum: Sum of item 2, 3, 4 (score range 0-11)
RS-Chest Symptom: Sum of item 1, 5, 6 (score range 0-12)

E-RS Total and Subscale scores will be computed for each day of diary collection. If no diary entry exists for a given day, missing values will be recorded. If the Total or Subscale score is 0, the value will be changed to missing. However, a 0 or missing Subscale doesn't impact the Total score calculation. This scoring rule is based on previous validation work demonstrating that moderate-to-severe COPD patients will experience symptom(s) each day, and a score of zero is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s).

RAW SCORE ASSIGNMENT

The following annotates the raw scale values associated with each response category for the R-RS items.

1. Did your chest feel congested today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
2. How often did you cough today?	0. Not at all
	1. Rarely
	2. Occasionally
	3. Frequently
	4. Almost constantly
3. How much mucus (phlegm) did you bring up when coughing today?	0. None at all
	1. A little
	1. Some
	2. A great deal
	3. A very great deal
	NOTE: Score "a little" and "some" the same.
4. How difficult was it to bring up mucus (phlegm) today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Quite a bit
	4. Extremely
5. Did you have chest discomfort today?	0. Not at all
	1. Slight
	2. Moderate
	3. Severe
	4. Extreme
6. Did your chest feel tight today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely

7. Were you breathless today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
8. Describe how breathless you were today:	0. Unaware of breathlessness
	1. Breathless during strenuous activity
	2. Breathless during light activity
	3. Breathless when washing or dressing
	3. Present when resting
	NOTE: Score "Breathless when washing or dressing" and "Present when resting" the same.
9. Were you short of breath today when performing your usual personal care activities like washing or dressing?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	4. Too breathless to do these
	NOTE: Score "severely" and "extremely" the same.
10. Were you short of breath today when performing your usual indoor activities like cleaning or household work?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	3. Too breathless to do these
	NOTE: Score "severely", "extremely", and "Too breathless to do these" the same.
11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	3. Too breathless to do these
	NOTE: Score "severely", "extremely", and "Too breathless to do these" the same.

6. REFERENCES

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