

Official Title: A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Astegolimab in Patients with Chronic Obstructive Pulmonary Disease

NCT Number: NCT05037929

Document Date: Statistical Analysis Plan Version 4: 24-Feb-2025

STATISTICAL ANALYSIS PLAN

STUDY TITLE: A PHASE IIb, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ASTEGOLIMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

STUDY NUMBER: GB43311

STUDY NAME: ALIENTO

VERSION NUMBER: 4

ROCHE COMPOUND: Astegolimab (RO7187807)

EUDRACT NUMBER: 2021-002045-15

IND NUMBER: 129714

NCT NUMBER: NCT05037929

PLAN PREPARED BY: [REDACTED] Ph.D.
[REDACTED] Ph.D.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

SPONSOR: Genentech, Inc.

LEGAL REGISTERED ADDRESS: Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

DATE FINAL: See electronic date stamp on the last page of this document

CONFIDENTIAL

This is a Genentech, Inc document that contains confidential information. Nothing herein is to be disclosed without written consent from Genentech, Inc.

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2.0

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
4	See electronic date stamp on the last page of this document	V 4.0, 27 October 2023
3	17 Jan 2025	V 4.0, 27 October 2023
2	7 June 2024	V 4.0, 27 October 2023
1	4 November 2022	V 2.0, 16 July 2021

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	Study populations were specified for each endpoint in the Type I Error control hierarchy.	To clarify the analysis population
Section 4.1	Baseline definition has been updated.	To improve clarity on the baseline definition.
Sections 4.2.2 and 4.3.1.3	The start date for time at risk and time to first COPD exacerbation calculation has been updated from the date of the randomization to the date of the first administration of the study treatment.	To ensure consistency between safety and efficacy analyses, as COPD exacerbation data is collected as an AE
Section 4.5.2	A safety analysis of the AE rate adjusted for patient-years at risk has been added.	To adjust for the exposure time in the AE rate so that the AE results are comparable with the other confirmatory study ARNASA.

All the changes made to Sections 2.1, 4.1, 4.2.2 and 4.3.1.3 were made for clarity purposes. Additional minor changes have been made throughout to improve clarity and consistency.

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE	3
1. INTRODUCTION.....	9
1.1 Objectives and Endpoints	9
1.2 Study Design	12
1.2.1 Treatment Assignment and Blinding	15
1.2.1.1 Treatment Assignment.....	15
1.2.1.2 Blinding	16
1.2.2 Independent Review Facility	16
1.2.3 Data Monitoring	16
2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION	17
2.1 Statistical Hypotheses	17
2.2 Sample Size Determination	18
3. ANALYSIS SETS	19
4. STATISTICAL ANALYSES	20
4.1 General Considerations	20
4.2 Primary Endpoint Analysis	21
4.2.1 Definition of Primary Endpoint	21
4.2.1.1 Primary Estimand	21
4.2.1.2 Secondary Estimand.....	22
4.2.2 Main Analytical Approach for Primary Endpoint(s).....	22
4.2.3 Sensitivity Analyses for Primary Endpoint	23
4.2.4 Supplementary Analyses for Primary Endpoint.....	24
4.2.4.1 Analyses excluding the patients impacted by IxRS incorrect assignment of treatment kits	24
4.2.4.2 Analysis excluding patients from sites with confirmed serious good clinical practice (GCP) non-compliance.....	24
4.2.4.3 Analysis handling deaths not related to COPD using composite strategy.....	24
4.2.4.4 Subgroup Analyses for Primary Endpoint	24
4.3 Secondary Endpoints Analysis(ses)	25

4.3.1	Key/Confirmatory Secondary Endpoints	25
4.3.1.1	Absolute change from baseline in SGRQ-C total score at Week 52	25
4.3.1.2	Absolute change from baseline in post-bronchodilator FEV ₁ (liters) at Week 52	27
4.3.1.3	Time to first moderate or severe COPD exacerbation	27
4.3.1.4	Annualized rate of severe COPD exacerbations over the 52-week treatment period	28
4.3.1.5	Absolute change from baseline in E-RS: COPD total score at Week 52.....	28
4.3.1.6	Proportion of patients with SGRQ-C improvement at Week 52	29
4.3.1.7	Absolute change from baseline in five-repetition sit-to- stand test (5STS) time (seconds) at Week 52	30
4.3.1.8	Subgroup analyses	30
4.4	Exploratory Endpoints Analysis	30
4.5	Safety Analyses	33
4.5.1	Extent of Exposure	33
4.5.2	Adverse Events.....	33
4.6	Other Analyses	34
4.6.1	Summaries of Conduct of Study	34
4.6.2	Summaries of Demographics and Baseline Characteristics	34
4.6.3	Pharmacokinetic Analyses.....	34
4.6.4	Immunogenicity Analyses	35
4.6.5	Biomarker Analyses.....	36
4.7	Interim Analyses	36
4.7.1	Planned Interim Analysis	36
4.8	Changes to Protocol-Planned Analyses	36
5.	SUPPORTING DOCUMENTATION.....	37
6.	REFERENCES.....	47

LIST OF TABLES

Table 1	Primary and Secondary Objectives and Corresponding Endpoints	9
Table 2	Exploratory Objectives and Endpoints	11
Table 3	Analysis Data Sets	19

LIST OF FIGURES

Figure 1	Study Schema.....	15
----------	-------------------	----

LIST OF APPENDICES

Appendix 1	Scoring of the St. George's Respiratory Questionnaire For COPD Patients (SGRQ-C)	38
Appendix 2	Scoring of the EXACT-Respiratory Symptoms (E-RS) scale	43

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
5STS	five-repetition sit-to-stand (test)
ADA	anti-drug antibody
AER	annualized exacerbation rates
ANCOVA	analysis of covariance
AUC	area under the concentration–time curve
CAT™	COPD Assessment Test™
CI	Confidence intervals
C _{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
CV	coefficient of variation
ECG	electro cardiogram
E-RS	Evaluating Respiratory Symptoms
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
GCP	Good Clinical Practice
H _a	alternative hypothesis
H ₀	null hypothesis
HR	hazard ratio
HRQoL	health-related quality of life
iDMC	independent Data Monitoring Committee
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
MAR	missing at random
mITT	modified intent-to-treat
MVPA	moderate and vigorous physical activity
N	population size
OLE	open-label extension
PD	pharmacodynamic
PK	pharmacokinetic

Q2W	once every 2 weeks
Q4W	once every 4 weeks
RR	rate ratio
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
SGRQ-C	St. George's Respiratory Questionnaire-COPD
SOC	standard of care
sST2	soluble ST2

1. **INTRODUCTION**

This statistical analysis plan (SAP) details the planned analyses and statistical methods for Study GB43311. The analyses described in this SAP will supersede those specified in Protocol GB43311 for the purposes of a regulatory filing.

Changes to the protocol-planned analyses are described in Section 4.8.

1.1 **OBJECTIVES AND ENDPOINTS**

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of astegolimab compared with placebo in patients with chronic obstructive pulmonary disease (COPD) who are former or current smokers and have a history of frequent exacerbations. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Primary and Secondary Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
To evaluate the efficacy of astegolimab compared with placebo in patients with COPD	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.

Secondary Objectives	Corresponding Endpoints
To evaluate the efficacy of astegolimab compared with placebo in patients with COPD	- Annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period in patients with low baseline blood eosinophil level (< 300 cells/μL) - Absolute change from baseline in HRQoL at Week 52, as assessed through the SGRQ-C total score - Absolute change from baseline in post-bronchodilator FEV₁ (liters) at Week 52 - Time to first moderate or severe COPD exacerbation during the 52-week treatment period - Annualized rate of severe COPD exacerbations over the 52-week treatment period - Absolute change from baseline in E-RS[®]:COPD total score at Week 52 - Proportion of patients with improvement in HRQoL, defined as a decrease from baseline of ≥ 4 points in SGRQ-C total score, at Week 52 - Absolute change from baseline in 5STS time (seconds) at Week 52
To evaluate the safety of astegolimab compared with placebo in patients with COPD	- Incidence and severity of adverse events, with severity 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 - Change from baseline in targeted vital signs, targeted 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

5STS= five-repetition sit-to-stand test; ADA= anti-drug antibodies; AIDS= acquired immunodeficiency syndrome; COPD= chronic obstructive pulmonary disorder; DAIDS= Division of AIDS; ECG= electro cardiogram; E-RS: COPD= Evaluating Respiratory Symptoms in COPD; FEV₁= forced expiratory volume in 1 second; HHS= Health and Human Services; HRQoL= health-related quality of life; IM= intramuscular; IV= intravenous; PK= pharmacokinetic; SGRQ-C= St. George's Respiratory Questionnaire-COPD.

Table 2 Exploratory Objectives and Endpoints

Exploratory Objectives	Corresponding Endpoints
To evaluate the efficacy of astegolimab compared with placebo	- Annualized rate of EXACT[®]–defined exacerbation events over the 52-week treatment period - An EXACT exacerbation event is defined as an EXACT total score of ≥ 12 points sustained for 2 days or ≥ 9 points sustained for 3 days. - Proportion of patients with HRQoL improvement, defined as a decrease from baseline of ≥ 4 points in SGRQ-C total score, at Week 12 and Week 24 - Proportion of patients 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 FEV₁ (liters) at Weeks 12, 24, and 36 - Absolute change from baseline in 5STS time (seconds) at Weeks 24 - 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 residual volume/total lung capacity ratio at Week 52 - Absolute change from baseline in daily step count at Weeks 12, 24, and 52

Exploratory Objectives	Corresponding Endpoints
To evaluate the efficacy of astegolimab compared with placebo (cont.)	- Absolute change from baseline in time in moderate and vigorous physical activity at Weeks 12, 24, and 52 - Absolute change from baseline in CAT™ score at Week 52 - Annualized rate of moderate and severe COPD exacerbations over the blinded treatment period - 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, or PK endpoints
To identify and/or evaluate biomarkers that are predictive of response to astegolimab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of astegolimab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	Relationship between biomarkers in blood, plasma, serum, and sputum and Nasosorption™ samples (listed in Sections 4.5.11 and 4.5.16 of the protocol) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

5STS= five-repetition sit-to-stand test; ADA=anti-drug antibodies; COPD=chronic obstructive pulmonary disorder; E-RS: COPD=Evaluating Respiratory Symptoms in COPD; FEV₁=forced expiratory volume in 1 second; PK=pharmacokinetic; SGRQ-C=St. George's Respiratory Questionnaire-COPD.

1.2 STUDY DESIGN

This is a Phase IIb, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety and PK of astegolimab in combination with standard of care (SOC); (defined in Section 4.3.2.2 of Protocol) compared with placebo in combination with SOC, in patients with COPD who are former or current smokers and have a history

Astegolimab—Genentech, Inc.

Statistical Analysis Plan GB43311

of frequent exacerbations. Approximately 1440 patients with COPD are expected to be enrolled globally.

Following a screening period of at least 7 days to up to 4 weeks, patients will be randomized in a 1:1:1 ratio to one of three 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 at least 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) once every 2 weeks (Q2W)
- Astegolimab 476 mg SC once every 4 weeks (Q4W)
 - To ensure that all study patients undergo the same visit schedule, patients randomized to the Q4W dosing arm will alternate between injections of astegolimab and placebo Q2W (beginning with astegolimab on Day 1), thus receiving astegolimab every 4 weeks.
- Placebo SC Q2W

Patients will return to the clinic Q2W through the treatment completion visit at Week 52 (or the end of an additional treatment period, as described below, if applicable). The primary endpoint analyses will be conducted using the 52-week treatment period data for all patients.

Patients will be enrolled in two phases. The initial study phase includes patients randomized until a sample size of approximately 1290 planned for the primary analysis is reached. During this phase, patients are given the option to participate in the intensive PK sampling (Section 4.5.15 of the protocol) and/or the Airway Biomarker Substudy (Section 4.5.16 of the protocol).

After the initial phase completes enrollment (i.e., approximately 1290 patients have been randomized), patients enrolled during the second study phase will complete the same assessments as those done during the initial study phase.

Patients in the second phase will additionally participate in the assessments outlined for at least one of the following:

- a) Intensive PK sampling (approximately n=60 in the second phase for a total of approximately n=240; Section 4.5.15 of the protocol) and
- b) Airway Biomarker Substudy (approximately n=90 in the second phase for a total of approximately n=100; Section 4.5.16 of the protocol).

All patients, regardless of the phase in which they are enrolled, will be subject to the same conduct of the protocol (e.g., stopping rules, assessments and their timing, access

to additional treatment period and/or open-label extension [OLE]) except for additional substudy assessments performed in patients either opting in or required based on phase of enrollment. However, the timing of interim and primary efficacy analyses will be based only on patients enrolled in the initial study phase.

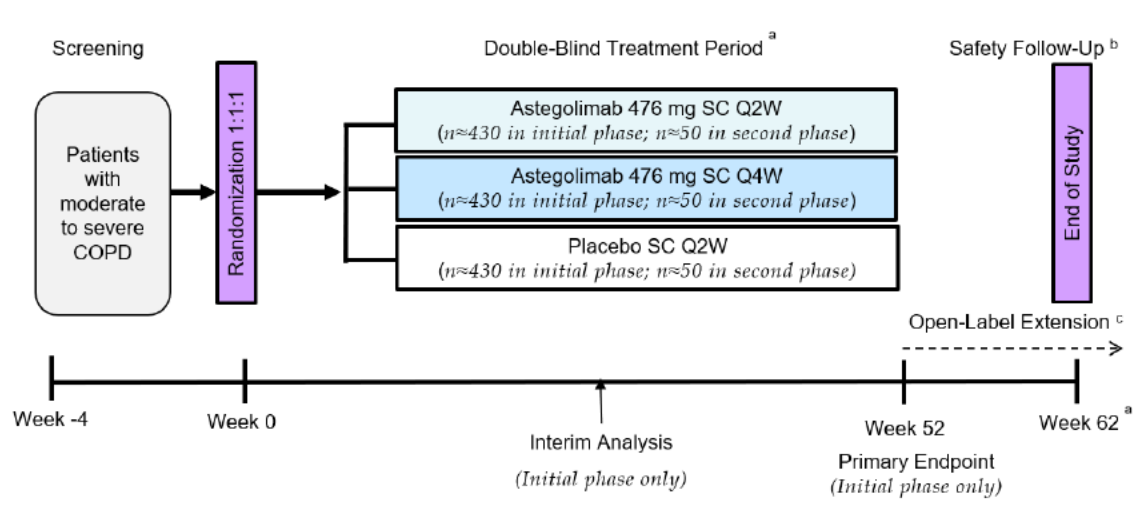
An independent Data Monitoring Committee (iDMC) will monitor patient safety during the study (see Section 3.1.4 of the protocol) and conduct an interim analysis for futility in the initial study phase. Patients who complete the Week 52 visit before the interim analysis will continue to receive blinded treatment beyond the 52-week treatment period for an additional 36 weeks or until the interim analysis results are known, whichever is sooner.

If a separate OLE study, Study GB43374, is open and available in their respective country, all patients 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 Section 3.1.2 of the protocol), or enter the safety follow-up period (see Section 3.1.3 of the protocol). If OLE Study GB43374 is not opened, all patients who complete the Week 52 visit, including those patients receiving continued blinded treatment after Week 52 visit may enter the additional treatment period until local availability of the OLE. If the OLE is not locally available or the patient does not enter the additional treatment period, patients who complete the Week 52 visit, will enter the safety follow-up period. All patients will undergo a safety follow-up visit 12 weeks after their final dose of study drug (regardless of the length of treatment received).

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion (see Section 4.5.1 of the protocol). The investigator will record reasons for screen failure in the screening log.

[Figure 1](#) presents an overview of the study design.

Figure 1 Study Schema



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

Note: During the initial phase of the study ($n \approx 1290$), patients have the option of participating in intensive PK sampling and/or the Airway Biomarker Substudy assessments. At least one of these assessments becomes a requirement for patients enrolling in the second phase of the study (after 1290 patients are enrolled). All patients are subject to 1:1:1 randomization and all other aspects of the study remain identical between study phases.

a Treatment for some patients may continue beyond the 52-week treatment period, as detailed in Section 3.1.1 of the protocol.

b Patients 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 Section 3.1.3 of the protocol.

c Patients enrolled in this study may have the opportunity to participate in OLE Study GB43374, if eligible, as detailed in Section 3.1.2 of the protocol.

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 patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of three 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.

1.2.1.2 Blinding

Study site personnel and patients 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 patient 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 iDMC members.

While PK and immunogenicity samples must be collected from patients assigned to the placebo arm to maintain the blinding of treatment assignment, PK and anti-drug antibody (ADA) assay results for these patients 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 patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the placebo 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 patients. Post-baseline immunogenicity samples from patients assigned to the placebo 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 patient 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 contact the Medical Monitor to discuss emergency unblinding after the treatment code has been broken.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7 of Protocol) that are considered by the investigator or Sponsor to be related to an investigational medicinal product (IMP; defined in Section 4.3 of Protocol). The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient 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 is planned for this study.

1.2.3 Data Monitoring

An iDMC will monitor safety data on an ongoing basis and conduct the planned interim analysis (see Section 6.9 of the protocol). 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. 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, and electro cardiogram (ECG) 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 $AER_{\text{treatment}}$ 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:

- $H_0: AER_{\text{treatment}} = AER_{\text{placebo}}$, or $RR = 1$, versus
- $H_a: AER_{\text{treatment}} \neq AER_{\text{placebo}}$, 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 annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period in patients with low baseline blood eosinophil level (< 300 cells/ μ L) and the secondary efficacy endpoints, 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. Annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period in patients with low baseline blood eosinophil level (< 300 cells/ μ L)
2. 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
3. Absolute change from baseline in post-bronchodilator forced expiratory volume in 1 second (FEV₁) (liters) at Week 52 in overall population
4. Time to first moderate or severe COPD exacerbation during the 52-week treatment period in overall population
5. Annualized rate of severe COPD exacerbations over the 52-week treatment period in overall population
6. Absolute change from baseline in Evaluating Respiratory Symptoms (E-RS) in COPD (E-RS[®]:COPD) total score at Week 52 in overall population
7. Proportion of patients with improvement in HRQoL, defined as a decrease from baseline of ≥ 4 points in SGRQ-C total score, at Week 52 in overall population
8. Absolute change from baseline in five-repetition sit-to-stand test (5STS) time (seconds) at Week 52 in overall population

2.2 SAMPLE SIZE DETERMINATION

In the initial phase of the study, a total of approximately 1290 patients 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 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 over dispersion parameter of 1.3.

For the second study phase, approximately 150 patients will continue to be randomly allocated in a 1:1:1 ratio to receive astegolimab Q2W, astegolimab Q4W, or placebo for at least one of the following assessments:

- a) Intensive PK sampling (approximately 60 patients) and
- b) Airway Biomarker Substudy (approximately 90 patients).

Due to the exploratory nature of the second study phase, no statistical powering is performed for this second study phase.

3. **ANALYSIS SETS**

The analysis populations presented in this section are based on patients enrolled during the initial study phase and will not include the second study phase, unless otherwise specified.

The analysis data sets for the purposes of analyses 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
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 measurable postdose PK assessment
Immunogenicity evaluable	All randomized participants with at least one post dose 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 after all enrolled patients in the initial study phase have either completed the 52-week treatment period or have discontinued from the study during the 52-week treatment period. Only patients from the initial phase will be included in the primary analyses. A clinical study report (CSR) based on the primary analyses may be prepared for the purpose of a regulatory filing. The final analyses will be exploratory and performed after all enrolled patients in both the initial and second phases have either discontinued the study, completed the study or have rolled over to the OLE study. All patients from both phases will be included in the final analyses. A separate CSR may be prepared based on final analyses.

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

All safety analyses will be performed in the safety evaluable population, 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.

Patient disposition will be summarized based on the ITT 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.

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.

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 Section 1.1.

4.2.1.1 Primary Estimand

The primary estimand is the RR in annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period between astegolimab and placebo patients.

The primary estimand is further described by the following attributes:

- 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
- Treatment:
 - Experimental: astegolimab Q2W
 - Experimental: astegolimab Q4W
 - Control: placebo
- 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 patients may continue in the study after the treatment discontinuation, all subsequent measurements after the prohibited medication use will be censored.
 - 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 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 in Section 1.1 as a severe

exacerbation and will not be counted twice when calculating the number of exacerbations.

- 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

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 patients 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 may be performed to assess the robustness of conclusion assuming data missing not at random.

4.2.1.2 Secondary Estimand

The annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period in participants with a low blood eosinophil level (< 300 cells/ μ L) will be analyzed as a secondary estimand. This secondary estimand is defined identically to the primary estimand, with the exception of the population. The population for this secondary estimand is defined as individuals with COPD who are former or current smokers, have a history of frequent exacerbations, and have a blood eosinophil level < 300 cells/ μ L. For the purpose of analysis, each patient's baseline value of blood eosinophil level will be used to determine if they have < 300 cells/ μ L. 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(s)

The unadjusted AER will be estimated as the total number of moderate and severe COPD exacerbations observed over the 52-week treatment period divided by the total patient-year at risk. All observed moderate and severe COPD exacerbations with an onset date during the 52-week treatment period will be included in the primary analysis. For each patient, the time at risk (in years) will be derived as the number of days from the date of the first administration of study drug to the date of study completion or discontinuation in the 52-week 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 and the stratification factors as specified in Section 4.1 as covariates. The natural log transformation of the patient'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 Analyses for Primary Endpoint

Sensitivity analysis using Poisson regression model and/or using baseline FEV₁ as an additional adjustment variable

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. A different model additionally adjusted for baseline FEV₁, i.e., one adjusted for baseline FEV₁ and the covariates described in Section 4.2.2, will also be used for both the Negative Binomial and Poisson regression model. 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 patient level for the observed period between the last study visit and Week 52 visit for patients who discontinued study 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 patient-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 for Primary Endpoint

4.2.4.1 Analyses excluding the patients impacted by IxRS incorrect assignment of treatment kits

At the early stage of the study, ten active patients were assigned treatments kits incorrectly due to misspecification of the IxRS dispensing schedule of the active and placebo kits (i.e., orders of active and placebo kits were reversed for all treatment arms). The IxRS dispensing error was corrected upon discovery. The 10 impacted patients had their planned treatment assignment updated in IxRS based on the treatment they received and continued the dosing schedule according to their corrected treatment assignment.

To assess impact of IxRS dispensing error, the primary analysis of the primary endpoint will be repeated with the ten impacted patients excluded from the mITT population.

4.2.4.2 Analysis excluding patients 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 patients from these sites excluded from the mITT population.

4.2.4.3 Analysis handling 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.

4.2.4.4 Subgroup Analyses for Primary Endpoint

The generalizability of the primary endpoint results when comparing astegolimab to placebo was 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/ μ L, < 300 cells/ μ L)
- Baseline blood eosinophil level (≥ 150 cells/ μ L, < 150 cells/ μ L)
- Baseline blood eosinophil level (≥ 300 cells/ μ L, ≥ 150 cells/ μ L to < 300 cells/ μ L, < 150 cells/ μ L)
- Number of COPD exacerbation in a 12-month period within the last 24 months (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: $FEV_1 \geq 50$ % predicted to < 80 % predicted; Severe: $FEV_1 \geq 30$ % 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 covariates 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 we run the analysis for patients who are current smokers, 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 ANALYSIS(SES)

4.3.1 Key/Confirmatory Secondary Endpoints

4.3.1.1 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 patient'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 estimand for this key secondary endpoint is defined as follows:

- Population: As defined for the primary endpoint in Section [4.2.1](#)
- Endpoint: Absolute change from baseline in HRQoL at Week 52, as assessed through the SGRQ-C total score
- Treatment: As defined for the primary endpoint in Section [4.2.1](#)
- Intercurrent events and the 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 leads to treatment discontinuation
 - Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy)
 - Other intercurrent events are handled the same as defined for the primary endpoint in Section [4.2.1](#)
- Population-level summary: difference in mean absolute change from baseline

The absolute change in SGRQ-C total score from baseline will be summarized by treatment arm and time-point. 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) to handle the missing data under MAR. 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, 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. A testing hierarchy will be used to control the overall Type I error rate at 5%, as described in Section [2.1](#).

4.3.1.2 Absolute change from baseline in post-bronchodilator FEV₁ (liters) at Week 52

Post-bronchodilator FEV₁ is defined as the FEV₁ value taken in the spirometry after the procedure for bronchodilator testing.

The estimand for this key secondary endpoint is defined as follows:

- Population: As defined for the primary endpoint in Section 4.2.1
- Endpoint: Absolute change from baseline in post-bronchodilator FEV₁ (liters) at Week 52
- Treatment: As defined for the primary endpoint in Section 4.2.1
- Intercurrent events and handling strategies: As defined for the SGRQ-C total score in Section 4.3.1.1
- Population-level summary: difference in mean absolute change from baseline

This key secondary endpoint will be analyzed in a similar manner as the SGRQ-C total score (see Section 4.3.1.1). A testing hierarchy will be used to control the overall Type I error rate at 5%, as described in Section 2.1 .

4.3.1.3 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. Patients who have not had an event will be censored at the end of their time at risk as defined in Section 4.2.2.

The estimand for this key secondary endpoint is defined as follows:

- Population: As defined for the primary endpoint in Section 4.2.1
- Endpoint: Time to first moderate or severe COPD exacerbation during the 52-week treatment period
- Treatment: As defined for the primary endpoint in Section 4.2.1
- Intercurrent events and handling strategies: As defined for the primary endpoint in Section 4.2.1.
- Population-level summary: hazard ratio (HR) for time to first moderate or severe COPD exacerbation

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 patients, unstratified analyses will be used as the primary analysis.

The 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% CI and associated p-values for the treatment effect will be calculated based on the model. A testing hierarchy will be used to control the overall Type I error rate at 5%, as described in Section 2.1 .

4.3.1.4 Annualized rate of severe COPD exacerbations over the 52-week treatment period

A severe COPD exacerbation is as defined in Section 1.1 .

This key secondary endpoint will be analyzed using the similar estimand as the primary endpoint (see Section 4.2.2). 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. All subsequent measurements after the prohibited COPD medication use will be censored. A testing hierarchy will be used to control the overall Type I error rate at 5%, as described in Section 2.1 .

4.3.1.5 Absolute change from baseline in E-RS: COPD total score at Week 52

The EXAcacerbations of Chronic Pulmonary Disease Tool (EXACT) is administered as a daily eDiary that assesses COPD exacerbations (Leidy et al. 2010). The 14-item questionnaire contains four domains: breathlessness (5 items), cough and sputum (3 items), chest symptoms (3 items), and additional attributes (3 items). A copy of the EXACT assessment is provided in Appendix 5 of the protocol. The subset E-RS:COPD is composed of the breathlessness, cough and sputum and chest symptoms domains (11 total items) of the EXACT questionnaire (Leidy et al. 2014). 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 scores, 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 E-RS: COPD total score.

The estimand for this key secondary endpoint is defined as follows:

- Population: As defined for the primary endpoint in Section 4.2.1
- Endpoint: Absolute change from baseline in E-RS: COPD total score at Week 52
- Treatment: As defined for the primary endpoint in Section 4.2.1

- Intercurrent events and handling strategies: Intercurrent events and handling strategies: As defined for the SGRQ-C total score in Section 4.3.1.1
- Population-level summary: difference in mean absolute change from baseline

This key secondary endpoint will be analyzed in a similar manner as the SGRQ-C total score (see Section 4.3.1.1). A testing hierarchy will be used to control the overall type I error rate at 5%, as described in Section 2.1.

4.3.1.6 Proportion of patients with SGRQ-C improvement at Week 52

The proportion of patient with SGRQ-C improvement (responder) is defined as the proportion of patients 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 4.3.1.1.

The estimand for this key secondary endpoint is defined as follows:

- Population: As defined for the primary endpoint in Section 4.2.1
- Endpoint: Patients with improvement in HRQoL, defined as a decrease from baseline of ≥ 4 points in SGRQ-C total score, at Week 52
- Treatment: As defined for the primary endpoint in Section 4.2.1
- Intercurrent events and handling strategies:
 - Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: All events will be treated under the composite strategy, since patients 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 leads to treatment discontinuation.
 - Death not related to COPD exacerbation: Data will be censored after the death occurrence (i.e., hypothetical strategy)
 - Other intercurrent events are handled the same as defined for the primary endpoint in Section 4.2.1
- Population-level summary: odds ratio of having SGRQ-C improvement

For patients without Week 52 data, their last available assessment of SGRQ-C will be used. Patients without post-baseline assessments will be excluded.

The proportion of patients with SGRQ-C improvement will be summarized by treatment arm and timepoint. The odds ratio of having SGRQ-C improvement at Week 52 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 will be calculated. A testing hierarchy will be used to control the overall type I error rate at 5%, as described in Section 2.1 .

4.3.1.7 Absolute change from baseline in five-repetition sit-to-stand test (5STS) time (seconds) at Week 52

The 5STS time (seconds) is defined as the time taken to stand up from a seated position five times, in as rapid succession as possible.

The estimand for this key secondary endpoint is defined as follows:

- Population: As defined for the primary endpoint in Section 4.2.1
- Endpoint: Absolute change from baseline in 5STS time (seconds) at Week 52
- Treatment: As defined for the primary endpoint in Section 4.2.1
- Intercurrent events and handling strategies: As defined for the SGRQ-C total score in Section 4.3.1.1
- Population-level summary: difference in mean absolute change from baseline

This key secondary endpoint will be analyzed in a similar manner as the SGRQ-C total score (see Section 4.3.1.1). A testing hierarchy will be used to control the overall Type I error rate at 5%, as described in Section 2.1.

4.3.1.8 Subgroup analyses

Subgroup analyses will also be performed for all key secondary endpoints based on subgroups defined in Section 4.2.4.4 . 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 we run the analysis for patients who are current smokers, smoker status (former vs current) will be removed as a covariate in the model.

4.4 EXPLORATORY ENDPOINTS ANALYSIS

- **Annualized Rate of EXACT Exacerbations over the 52-week treatment period**

See Section 4.3.1.5 for the introduction of the EXACT. The annualized rate of EXACT exacerbation events is defined as an EXACT total score of ≥ 12 points sustained for 2 days or ≥ 9 points sustained for 3 days. For the exacerbation analysis, the baseline would be reset during the study. Additional information related to computing scores and frequency, severity, and duration of events can be found in the EXACT patient reported outcome (PRO) User Manual Version 7.0. This exploratory endpoint will be analyzed in a similar manner as the primary endpoint (see Section 4.2.2).

- **Proportion of Patients with SGRQ-C Improvement at Week 12 and Week 24**

Proportion of patients with SGRQ-C improvement is defined as described in Section 4.3.1.6. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of proportion of patients with SGRQ-C improvement at Week 52 (see Section 4.3.1.6).

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

The proportion of patients E-RS:COPD improvement is defined as the proportion of patients 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 patients with SGRQ-C improvement at Week 52 (see Section 4.3.1.6).

- **Absolute Change in Post-bronchodilator FEV₁ at Weeks 12, 24, and 36**

This exploratory endpoint is defined as the secondary endpoint of absolute change from baseline in post-bronchodilator FEV₁ at Week 52 (see Section 4.3.1.2). It will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C at Week 52 (see Section 4.3.1.1).

- **Absolute Change in 5STS time at Week 24**

The 5STS time is defined by the amount of time (to the nearest decimal in seconds) a patient is able to transfer from a seated to a standing position and back to sitting five times. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C at Week 52 (see Section 4.3.1.1).

- **Annualized Rate of Moderate 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, 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).

- **Duration of Hospital Stay for Severe COPD Exacerbations**

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 patients 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 patient'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 Residual Volume/Total Lung Capacity Ratio at Week 52**

The ratio is calculated by residual volume divided by the total lung capacity. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C at Week 52 (see Section 4.3.1.1) except that the statistical model will be using analysis of covariance (ANCOVA) rather than MMRM. No missing data will be imputed.

- **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 at Week 52 (see Section 4.3.1.1).

- **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 at Week 52 (see Section 4.3.1.1).

- **Absolute Change in COPD Assessment Test™(CAT™) score at Week 52**

The CAT™ score is an 8-item questionnaire that includes items related to cough, phlegm, chest tightness, breathlessness ascending hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy. The CAT™ uses a 6-point ordinal scale, ranging from 0 (no impairment) to 5 (maximum impairment), with a score range of 0-40 and higher scores indicating a greater disease impact. A copy of the assessment is provided in Appendix 7 of the protocol. The CAT™ total score is calculated by summing the individual scores from the 8 items. This exploratory endpoint will be analyzed in a similar manner as the secondary endpoint of absolute change from baseline in SGRQ-C at Week 52 (see Section 4.3.1.1) except that the statistical model will be using ANCOVA rather than MMRM. No missing data will be imputed.

- **Annualized Rate of Moderate and Severe COPD Exacerbations over the Blinded Treatment Period**

Before the planned interim analysis for futility, patients who complete the Week 52 visit can choose to continue to receive blinded treatment beyond the 52-week treatment period for an additional 36 weeks or until the interim analysis results are known, whichever is sooner (see Section 3.1.1 of the protocol). Moderate and severe COPD exacerbations, as defined in Section 4.2.1, occurred the additional

treatment period will be counted in addition to the ones in the 52-week treatment period. For each patient, the time at risk (in years) will be derived as the number of days from the date of randomization to the date of study completion or discontinuation in the 52-week treatment period and the additional treatment period, divided by 365.25 days. This exploratory endpoint will be analyzed in a similar manner as the primary endpoint (see Section 4.2.2).

- **Overall survival, defined as the time from randomization to death from any cause during the patient's study participation (i.e., deaths occurring after the safety follow-up or after the patient 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 4.3.1.3).

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 patients.

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 Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to the Division of acquired immunodeficiency syndrome (AIDS) (DAIDS) Table v2.1 (see Appendix 8 of the protocol). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, adverse events leading to discontinuation from study treatment and adverse events leading to discontinuation from study will be summarized by treatment groups. A treatment-emergent adverse event is defined as any new adverse event reported or worsening of an existing condition on or after the first dose of study drug. 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.

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, potential risks, and 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 patients 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. Additionally, there will be a PK analysis subset, which includes all subjects who completed the intensive PK sampling Substudy and had sufficient data to enable estimation of key parameters (e.g., area under the concentration-time curve [AUC], time to maximum concentration [$t_{\max}$], maximum concentration [$C_{\max}$], half-life).

For both main study and PK Substudy, 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. In addition, for PK Substudy, individual and overlay plots of individual serum astegolimab concentration profiles will be generated for all subjects by treatment.

The serum PK parameters of astegolimab will be summarized as measured by AUC, C_{max} , total clearance, volume of distribution at steady state, and terminal half-life, as appropriate for data collected. Estimates for these parameters will be tabulated and summarized (including N, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric mean CV%). Drug accumulation will be evaluated. 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.

Pharmacokinetic analysis will use actual times, if available. If actual times are missing, nominal times may be used or data with missing collection times may be excluded.

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 patients with at least one post-dose ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients 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 one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients 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 patients 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, FEV₁) to assess if a subset of patients 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 patients 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.

4.7 INTERIM ANALYSES

4.7.1 Planned Interim Analysis

An interim analysis for futility will be conducted by the iDMC after approximately 210 patients have experienced at least one moderate to severe exacerbation event in the study. The interim analysis will be conducted as described in the [Interim Statistical Analysis Plan](#).

4.8 Changes to Protocol-Planned Analyses

The planned statistical model of the primary objective in the protocol is Poisson regression with overdispersion, and it has been updated to Negative Binomial regression model in the SAP. Poisson regression with overdispersion will be a sensitivity analysis. Literature has shown that Negative Binomial regression may provide an improved model for exacerbation rate data compared with Poisson regression ([Metcalf and Thompson 2005](#)).

In addition, a secondary estimand for the primary endpoint in the in patients with low baseline blood eosinophil level (< 300 cells/ μ L) has been added in the SAP to test the

hypothesis of astegolimab's treatment effect in the patients with low baseline eosinophil level.

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:

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

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:

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

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 patient 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 chronic obstructive pulmonary disease (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
4. How difficult was it to bring up mucus (phlegm) today?	NOTE: Score "a little" and "some" the same.
	0. Not at all
	1. Slightly
	2. Moderately
	3. Quite a bit
5. Did you have chest discomfort today?	4. Extremely
	0. Not at all
	1. Slight
	2. Moderate
	3. Severe
6. Did your chest feel tight today?	4. Extreme
	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
	<i>NOTE: Score "Breathless when washing or dressing" and "Present when resting" the same.</i>
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
	<i>NOTE: Score "severely" and "extremely" the same.</i>
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
	<i>NOTE: Score "severely", "extremely", and "Too breathless to do these" the same.</i>
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
	<i>NOTE: Score "severely", "extremely", and "Too breathless to do these" the same.</i>

6. REFERENCES

- Interim Statistical Analysis Plan GB43311 – A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Astegolimab in Patients with Chronic Obstructive Pulmonary Disease. April 2023.
- Jones WP. St. George's Respiratory Questionnaire: MCID, COPD; 2005 Mar, 2(1):75-79.
- Leidy NK, Murray LT, Monz BU, et al. Measuring respiratory symptoms of COPD: performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials. *Respir Res* 2014;15(1):124.
- Leidy NK, Wilcox TK, Jones PW, et al., EXACT-PRO Study Group. Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO) measure. *Value Health* 2010;13(8):965–75.
- Meguro M, Barley EA, Spencer S, et al. Development and validation of an improved, COPD-specific version of the St. George Respiratory Questionnaire. *Chest* 2007;132(2):456–63.
- Metcalf C, Thompson SG. The importance of varying the event generation process in simulation studies of statistical methods for recurrent events. *Statistics in medicine*. 2006 Jan 15;25(1):165-79.
- Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. *Pharmaceutical statistics*. 2014 Jul;13(4):258-64.

Signature Page for Statistical Analysis Plan - GB43311 - Published

System identifier: RIM-CLIN-997879

Approval Task	 Company Signatory 24-Feb-2025 19:01:23 GMT+0000
---------------	---