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: Protocol Amendment Version 4: 27-Oct-2023

PROTOCOL

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**
PROTOCOL NUMBER:	GB43311
VERSION NUMBER:	4
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 129714 EU CT Number: 2023-507093-40-00 EUDRACT Number: 2021-002045-15
TEST PRODUCT:	Astegolimab (RO7187807)
SPONSOR NAME AND ADDRESS:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol		Associated Region-Specific Protocols		
Version	**Date Final**	**Region**	**Version**	**Date Final**
4	See electronic date stamp on final page.	—	—	—
3	30 January 2023	—	—	—
2	16 July 2021	VHP	1	18 October 2021
1	22 April 2021	—	—	—

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GB43311 has been amended to enroll approximately 150 additional patients for further characterization of pharmacokinetics and exploratory biomarkers. Updates have also been made to align with Clinical Trials Regulation (CTR) requirements. Changes, along with a rationale for each change, are summarized below:

- The synopsis has been simplified to align with CTR and other guidelines.
- The summary of astegolimab clinical studies has been updated with the latest data (Section 1.2.3).
- An overall survival exploratory endpoint, to understand time to death for all-cause mortality during the study treatment period, has been added (Section 2.1.3).
- To further characterize the pharmacokinetics and biology of astegolimab, approximately 150 additional patients will be enrolled after the initial phase of the study has completed enrollment (approximately 1290 patients). Consent to participate in at least one of the optional exploratory assessments (intensive pharmacokinetic (PK) sampling and the Airway Biomarker Substudy) is now required for patients who enroll in the second phase of the study (Sections 3.1.1, 3.2, 3.3.5, 4.5.15, 4.5.16, 6, 6.1, 6.5, 6.9, and 6.10; Appendix 1; Appendix 3).

  Other than the change from optional to required assessments and the timing of the interim and primary efficacy analyses, there are no other changes in study conduct for these additional patients.

  Patients enrolled in the second phase of the study who do not complete the intensive PK sampling or Airway Biomarker Substudy assessments may be replaced.
- A section describing patient input into the study design has been added to align with CTR requirements (Section 3.1.5).
- A comprehensive list of investigational, auxiliary, and non-investigational medicinal products has been added to align with CTR requirements (Section 4.3 and Appendix 9).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information in Section 5.4.1 has been replaced with a sentence indicating that this information will be provided separately to sites.
- To align with CTR requirements, text has been modified to clarify that summaries of clinical study results may be available for public access in health authority databases (Sections 8.4 and 9.6).
- The number of required sputum samples collected in the Airway Biomarker Substudy has been reduced (Appendix 1) in order to reduce site burden while ensuring critical samples are collected.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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TEST PRODUCT:	Astegolimab (RO7187807)
SPONSOR NAME AND ADDRESS:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

PROTOCOL SYNOPSIS

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**
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TEST PRODUCT:	Astegolimab (RO7187807)
PHASE:	IIb
INDICATION:	Chronic obstructive pulmonary disease
SPONSOR:	Genentech, Inc.

PRIMARY AND SECONDARY OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics 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.

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 $\geq$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	• Time to first moderate or severe COPD exacerbation during the 52-week treatment period • Absolute change from baseline in HRQoL at Week 52, as assessed through the SGRQ-C total score • Proportion of patients with improvement in HRQoL, defined as a decrease from baseline of $\geq$4 points in SGRQ-C total score, at Week 52 • 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 • Annualized rate of severe COPD exacerbations over the 52-week treatment period • 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; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disorder; DAIDS = Division of AIDS; E-RS:COPD = Evaluating Respiratory Symptoms in COPD; EXACT = EXAcerbations of Chronic Pulmonary Disease Tool; FEV_1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life; IM = intramuscular; SGRQ-C = St. George's Respiratory Questionnaire-COPD.

OVERALL DESIGN AND STUDY POPULATION

This Phase IIb, randomized, double-blind, placebo-controlled, multicenter study will evaluate the efficacy, safety, and pharmacokinetics of astegolimab in combination with standard of care (SOC) compared with placebo in combination with SOC in patients with COPD who are former or current smokers and have a history of frequent exacerbations.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase IIb	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	COPD
Interventional Model:	Parallel	**Population Age:**	40– 90 years
Test Compound:	Astegolimab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Randomized
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 1440

STUDY TREATMENT

ASTEGOLIMAB

Patients randomized to the astegolimab treatment arms will be administered one of the following dosing regimens:

- Astegolimab 476 mg SC every 2 weeks (Q2W)
- Astegolimab 476 mg SC 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 every 2 weeks (beginning with astegolimab on Day 1), thus receiving astegolimab every 4 weeks.

Each dose of astegolimab will be administered as two SC injections ([redacted]), with each injection administered on a different side of the abdomen (i.e., right or left).

PLACEBO

Patients in the placebo (control) arm will be administered each dose of placebo as two SC injections Q2W, with each injection administered on a different side of the abdomen (i.e., right or left).

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Standard-of-care COPD maintenance therapies, having been used prior to screening and continued throughout the study, are considered non-investigational medicinal products (NIMPs). Standard-of-care COPD maintenance therapy is defined as one of the following combinations:

- Inhaled corticosteroid (ICS) plus long-acting beta-agonist (LABA)
- Long-acting muscarinic antagonist (LAMA) plus LABA
- ICS, LAMA plus LABA

DURATION OF PARTICIPATION

The study will consist of a screening period of at least 7 days and up to 4 weeks, a treatment period of 52 weeks, and a safety follow-up period of 12 weeks. The total duration of study participation for each subject is expected to be approximately 1–66 weeks.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5STS	five-repetition sit-to-stand (test)
ADA	anti-drug antibody
AER	annualized exacerbation rate
AHR	airway hyperresponsiveness
ATS	American Thoracic Society
AUC	area under the concentration–time curve
CAT™	COPD Assessment Test™
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
DAIDS toxicity grading scale	Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eDiary	electronic diary
ERS	European Respiratory Society
E-RS®:COPD	Evaluating Respiratory Symptoms in COPD
EXACT®	EXAcerbations of Chronic Pulmonary Disease Tool
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HBA_{1c}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
iDMC	independent Data Monitoring Committee
IIS	investigator-initiated study
IL-1	interleukin-1
IL-1RL1	IL-1 receptor-like 1
IL-33	interleukin-33
IM	intramuscular
IMP	investigational medicinal product

Abbreviation	Definition
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
LABA	long-acting β-agonist
LAMA	long-acting muscarinic antagonist
MACE	major adverse cardiovascular event
mITT	modified intent-to-treat
mMRC	Modified Medical Research Council (dyspnea scale)
MN	mobile nursing
NGS	next-generation sequencing
NK	natural killer (cell)
OLE	open-label extension
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
SARS	severe acute respiratory syndrome
SARS-CoV-2	SARS coronavirus-2
SGRQ-C	St. George's Respiratory Questionnaire-COPD
SOC	standard of care
sST2	soluble ST2
Th2	T helper type 2 (cell)
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) was the third leading cause of death globally in 2019, causing approximately 6% of the world's total deaths (WHO Factsheet 2020). The WHO estimates that 65 million people currently have moderate to severe COPD (WHO 2021). Development of COPD is attributed to long-term exposure to inhaled cigarette smoke or noxious particles such as smoke from biomass fuels. Although cigarette smoking has traditionally been the single most important risk factor for COPD, there is consistent evidence that non-smokers can also develop COPD (Lamprecht et al. 2011). The risk of COPD increases with age and usually occurs in patients aged older than 40 years; the prevalence is greater among men than women (Landis et al. 2014).

COPD is characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar abnormalities, usually as a result of significant exposure to noxious gases or particles (GOLD 2021). The chronic airflow limitation is caused by a mixture of small airways diseases and parenchymal destruction (emphysema), which may be associated with narrowing of small airways and decreased lung elastic recoil (GOLD 2021). Clinically, the characteristic symptoms of COPD can include dyspnea, cough, and sputum production. COPD is a heterogeneous and progressive disease, with progression being strongly associated with airway-wall thickening and airflow limitation. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has introduced a classification of airflow limitation severity based on measurements of the forced expiratory volume in 1 second (FEV_1) and by the ratio of FEV_1 to the forced vital capacity (FVC). This assessment has been widely accepted as a key marker for disease progression (Hogg et al. 2004, Celli et al. 2008, GOLD 2021).

Another key marker of disease activity is COPD exacerbation, defined as an acute worsening of respiratory symptoms that result in additional therapy (GOLD 2021). While there exists some variability in the definition of exacerbation severity, severity is often classified as mild (increase in respiratory symptoms controllable by an increase of usual medication), moderate (requiring treatment with systemic corticosteroids and/or antibiotics), or severe (requiring hospitalization) (Solem et al., 2013, GOLD 2021). An increasing rate of COPD exacerbations is associated with decline in lung function, reduced quality of life, and death (Miravitlles et al. 2004. Halpin et al. 2012). Although the frequency of exacerbations increases with the severity of disease (Halpin et al. 2012), exacerbations affect individuals even with moderate COPD. Prior history of exacerbation, rather than airflow limitation, is the single best predictor for increased risk of future exacerbations (Hurst et al. 2010). COPD exacerbations are not only a major cause of morbidity and mortality, but also account for the greatest proportion of the total COPD healthcare costs (AbuDagga et al. 2013, Solem et al. 2013).

Current treatment options for COPD include non-pharmacologic and pharmacologic measures. Smoking cessation is a vital intervention for patients who continue to smoke and has the greatest potential impact on the natural course of COPD. Pulmonary rehabilitation similarly represents an important intervention for people with COPD, yet application remains low due to a variety of factors, including transportation, cost, and access. Pharmacologic treatment options include inhaled bronchodilators (beta-agonists and anti-cholinergics), inhaled and systemic corticosteroids, azithromycin, and phosphodiesterase inhibitors (GOLD 2021). Despite these treatment options, deceleration of disease progression and prevention of COPD exacerbations are still unmet needs (Patalano et al. 2014, Diette et al. 2015). Alternative and more effective therapeutic approaches that will relieve patient symptoms and alter the disease trajectory are urgently needed (Cazzola et al. 2016).

1.2 BACKGROUND ON ASTEGOLIMAB

Astegolimab (also known as RO7187807 or MSTT1041A) is a fully human, IgG2 monoclonal antibody that binds with high affinity to the IL-33 receptor, ST2, thereby blocking the signaling of interleukin-33 (IL-33), an inflammatory cytokine of the interleukin-1 (IL-1) family and member of the “alarmin” class of molecules. Astegolimab has subnanomolar affinity and potency, is active in blood, and lacks agonistic activity.

Refer to the Astegolimab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Background on Interleukin-33 and ST2

IL-33 is considered an "alarmin" or a damage-associated molecular pattern molecule that is constitutively expressed on epithelial cells and released upon cell injury or stress from exposure to such exogenous stimuli as allergens, toxins, or infections. IL-33 is a member of the IL-1 family of cytokines (Sims and Smith 2010) with potential as a target in the treatment of asthma, COPD, and atopic dermatitis.

High levels of IL-33 are found in stromal cells, particularly at barrier surfaces such as the lung and gastrointestinal tract. Within the lung, IL-33 is detected in multiple cell types, including epithelial cells, endothelial cells, and fibroblasts (Liew et al. 2016). IL-33 bioavailability is tightly regulated, and under homeostatic conditions, this protein is sequestered in the nuclei of these cells. Cellular damage caused by injury, mechanical stress, or death leads to the release of bioactive IL-33 into circulation, where it initiates and propagates innate and adaptive immune responses. The receptor for IL-33, ST2, is expressed on multiple cell types implicated in pulmonary inflammation and disease, including mast cells, eosinophils, basophils, innate lymphoid cells, T lymphocytes, macrophages, and endothelial cells.

IL-33 is also linked to the function of type-2 innate lymphocytes that accumulate in the lung and promote T helper type 2 (Th2) cell inflammation, even in the absence of antigen stimulation (Scanlon and McKenzie 2012). In some settings, IL-33 will also

promote type 1 responses, such as interferon (IFN)-γ production from natural killer (NK) cells or NK T cells. As such, IL-33 may be involved in multiple inflammatory pathways implicated in COPD.

IL-33 activates these various immune cells through its receptor ST2, also known as Il-1 receptor-like 1 (IL-1RL1) (Nabe 2014). The binding of IL-33 to ST2 promotes association with the shared IL-1 family subunit, IL-1RAcP, to form the active IL-33 receptor. Intracellular signaling induced by IL-33 promotes expression of inflammatory genes. A secreted soluble form of ST2 (sST2) arises from alternative splicing, is elevated in settings of inflammation, and acts as a decoy to bind and inhibit released IL-33 (Hayakawa et al. 2007).

Excess extracellular IL-33 is highly inflammatory in pulmonary tissue and is capable of triggering local inflammation that can lead to airway hyperresponsiveness (AHR) and mucus production, important components of exacerbations. Airway administration of IL-33 in mice leads to an infiltration of inflammatory cells in bronchoalveolar lavage fluid, including eosinophils and neutrophils, as well as elevated interleukin-5, interleukin-13, eotaxin, and thymus and activation-regulated chemokine (also known as TARC/CCL17) (Louten et al. 2011). Given the diverse nature of signals that lead to IL-33 release and the wide range of target cells, IL-33 is implicated in a number of pathological pathways. IL-33 release can trigger acute exacerbations and/or disease progression in asthma, COPD, idiopathic pulmonary fibrosis, and acute respiratory distress syndrome. IL-33 activity is elevated following viral infections, and inhibition of this pathway reduces virus-induced exacerbations in rodent models of asthma and COPD (Werder et al. 2018; Ravanetti et al. 2019). ST2- or IL-33–deficient mice exposed to cigarette smoke have decreased inflammatory responses in response to subsequent respiratory viral infections, without compromising anti-viral host defense (Kearley et al. 2015). The absence of the IL-33 pathway significantly reduced viral-induced leukocyte migration into the lung, inflammatory cytokine expression, and subsequent pulmonary pathology. For these reasons, inhibiting ST2 is hypothesized to confer clinical benefit to patients with COPD by limiting excessive inflammatory sequelae.

1.2.2 Summary of Nonclinical Studies

The toxicology program was designed to support IV and SC administration of astegolimab in clinical studies. Astegolimab has been shown to have a favorable overall nonclinical safety profile. In 28-day and 6-month repeat-dose toxicity studies, no adverse effects were observed in cynomolgus monkeys following biweekly IV or SC administration at doses up to 300 mg/kg (the highest dose tested). There were no adverse findings at the injection sites, as evidenced by macroscopic and microscopic analysis following SC administration at doses up to 300 mg/kg. In an ex vivo human tissue cross-reactivity study, biotin-labeled astegolimab staining was not observed in any human tissues evaluated by immunohistochemistry.

Refer to the Astegolimab Investigator's Brochure for details on nonclinical studies.

1.2.3 Summary of Clinical Studies

As of *10 February 2023*, 653 patients with asthma, *726 patients* with COPD *(645/726* from the ongoing/blinded *Studies* GB43311 and *GB44332*), 1 patient with chronic rhinosinusitis with nasal polyps, 410 patients with *severe* COVID-19 pneumonia, *65 patients with atopic dermatitis,* and 145 healthy subjects have been enrolled into astegolimab clinical studies. The safety profile of astegolimab demonstrated by these studies is summarized in the following section.

Refer to the Astegolimab Investigator's Brochure for details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

COPD is recognized as a progressive, heterogeneous disease. COPD exacerbations represent the largest burden in terms of healthcare utilization, patient morbidity, and risk of mortality (Anzueto 2010). Therefore, interventions that target the reduction of COPD exacerbations are expected to have the most benefit for patients with COPD. Despite a large unmet need, there are currently limited options for pharmacotherapy specifically targeted at reducing exacerbations.

COPD exacerbations can have a variety of underlying factors, including bacterial, viral, eosinophilic, or pollution-related. As detailed in Section 1.2.1, excess extracellular IL-33 is highly inflammatory in pulmonary tissue and is capable of triggering local inflammation that can lead to AHR and mucus production, important components of exacerbations. The role of the IL33/ST2 axis in COPD remains uncertain. However, a mouse model demonstrated increased IL-33 expression following viral infection, and lung tissues from patients with very severe COPD had significant increases in both IL33 mRNA and IL-33 protein levels when compared with lung tissue from patients without COPD, thus suggesting IL-33 may play a role in the consequent inflammatory response and possible susceptibility to secondary viral infection in obstructive lung disease (Byers et al. 2013). Therefore, targeting the IL33/ST2 axis might reduce COPD exacerbations.

Astegolimab, an anti-ST2 monoclonal antibody that acts as a pure, competitive antagonist to block IL-33 signaling, is hypothesized to have the potential to treat COPD by reducing exacerbations without inhibiting the development of protective adaptive immunity and viral clearance (Kearley et al. 2015). Nonclinical and clinical studies have demonstrated that astegolimab has a well-tolerated safety profile, and clinical studies of astegolimab have demonstrated reductions in asthma and COPD exacerbations. Therefore, astegolimab has potential for efficacy to treat COPD, supporting further clinical development. To date, there are no identified risks associated with astegolimab.

Although not observed in the one ongoing or six completed clinical trials to date, as with all protein therapies, there is the possibility that administration of astegolimab may lead to the development of anti-astegolimab antibodies, which could lead to adverse events and/or decreased exposure. To date, the immunogenicity rates observed with astegolimab have ranged from 3% to 27% (in the five completed clinical studies in which

ADA data was available), and there has been no correlation with clinical findings or adverse events. Monoclonal antibodies such as astegolimab carry a potential risk of hypersensitivity reactions and anaphylaxis or hypersensitivity-like reactions. Nevertheless, in completed astegolimab studies, rates of hypersensitivity and anaphylaxis or hypersensitivity-like reactions attributed to study drug have been much less than 1%, with only 1 patient in an astegolimab arm having experienced hypersensitivity across all studies to date.

The intended mechanism of action of astegolimab suggests inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of a decrease in the protective response to infection, particularly helminthic infections. Despite this possibility, no imbalance in infections, including helminthic infections, has been seen to date across the clinical trials.

Finally, in mice models of cardiovascular disease, a protective role for IL-33/ST2 has been described; mice genetically deficient in ST2 had more left ventricular hypertrophy, more fibrosis, and impaired survival relative to their wild-type littermates in an experimentally induced acute left ventricular pressure overload model. However, the translatability of those findings to humans remains unknown, and in addition, studies with conflicting data exist (Demyanets et al. 2011; Abston et al. 2012; Martin et al. 2015). Safety pharmacology studies in cynomolgus monkeys found no biologically significant cardiovascular effects of astegolimab. In the completed Phase II studies with astegolimab, none of the reported potential major adverse cardiovascular events (MACE) were considered related to study drug. No cases of potential MACE were reported in the three completed Phase I astegolimab studies.

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with COPD, are a more vulnerable population. Having COPD is known to increase the risk of severe illness from COVID-19. Astegolimab was evaluated in Study GA42469 in patients with severe COVID-19 pneumonia and was not found to adversely impact the severity of COVID-19. Based on the mechanism of action of astegolimab and preliminary analysis of Study GA42469, it is anticipated that astegolimab will not increase the risk of infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or facilitate a worse outcome in patients with COVID-19. The pattern of adverse events observed with astegolimab in Study GA42469 is consistent with patterns expected in a population of patients with severe COVID-19 pneumonia. Therefore, astegolimab is not expected to increase the risk from SARS-CoV-2 in patients with COPD.

Combined, nonclinical and clinical studies have demonstrated that astegolimab has a well-tolerated safety profile and strong rationale supporting its potential benefit in patients with COPD who have frequent exacerbations, supporting further clinical development in this indication. The potential risks for astegolimab will be mitigated by

safety monitoring and enrollment criteria that limit participation of patients with a history of unstable cardiac disease, recent myocardial ischemia, or severe heart failure.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of astegolimab compared with placebo in patients with 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.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo on the basis of the following 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 $\geq$ 3 days) with systemic corticosteroids (oral, IV, or intramuscular [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.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo on the basis of the following endpoints:

- Time to first moderate or severe COPD exacerbation during the 52-week treatment period
- 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
- Proportion of patients with improvement in HRQoL, defined as a decrease from baseline of $\geq$ 4 points in SGRQ-C total score, at Week 52
- Absolute change from baseline in post-bronchodilator FEV_1 (liters) at Week 52
- Absolute change from baseline in Evaluating Respiratory Symptoms in COPD (E-RS®:COPD) total score at Week 52
- Annualized rate of severe COPD exacerbations over the 52-week treatment period
- Absolute change from baseline in five-repetition sit-to-stand test (5STS) time (seconds) at Week 52

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo on the basis of the following endpoints:

- Annualized rate of EXAcerbations of Chronic Pulmonary Disease Tool (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 FEV_1 (liters) at Weeks 12, 24, and 36
- Absolute change from baseline in 5STS time (seconds) at Week 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
- Absolute change from baseline in time in moderate and vigorous physical activity at Weeks 12, 24, and 52
- Absolute change from baseline in COPD Assessment Test™ (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 during the study treatment period*

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of astegolimab compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the Division of AIDS (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 Section 5.3.3 and Appendix 8)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results and ECGs

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize the astegolimab PK profile on the basis of the following endpoint:

- Serum concentration of astegolimab at specified timepoints

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of astegolimab on the basis of the following endpoints:
  - 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 on the basis of the following endpoint:
  - Relationship between selected covariates and serum concentration or PK parameters for astegolimab

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to astegolimab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is 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, on the basis of the following endpoint:

- Relationship between biomarkers in blood, plasma, serum, and sputum and nasosorption™ samples (listed in Sections 4.5.11 and 4.5.16) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase IIb, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of astegolimab in combination with standard of care (SOC; defined in Section 4.3.2.2) compared with placebo in combination with SOC, in patients with COPD who are former or current smokers and have a history 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 SC every 2 weeks (Q2W)
- Astegolimab 476 mg SC 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 every 2 weeks (beginning with astegolimab on Day 1), thus receiving astegolimab every 4 weeks.
- Placebo SC Q2W

Patients will return to the clinic every 2 weeks 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) and/or the Airway Biomarker Substudy (Section 4.5.16).

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) and (b) Airway Biomarker Substudy (approximately n=90 in the second phase for a total of approximately n=100; Section 4.5.16).

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 (as described in Section 6) will be based only on patients enrolled in the initial study phase.

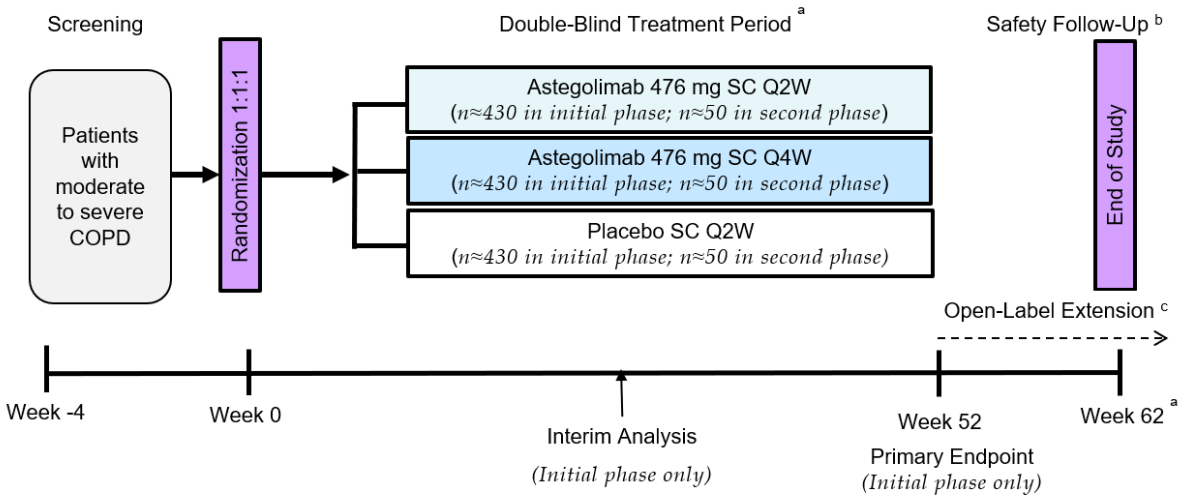
An independent Data Monitoring Committee (iDMC) will monitor patient safety *in both phases of* the study (see Section 3.1.4) and conduct an interim analysis for futility (see Section 6.9) *in the initial study phase*.

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), or enter the safety follow-up period (see Section 3.1.3). If OLE Study GB43374 is not opened, all patients who complete the 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 two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion (see Section 4.5.1). The investigator will record reasons for screen failure in the screening log.

Figure 1 presents an overview of the study design. Schedules of activities are provided in Appendix 1 and Appendix 2.

Figure 1 Study Schema



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

Note: During the initial phase of the study (n≈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.

[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.

[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.

3.1.2 Open-Label Extension Study GB43374

A separate open-label extension study for Study GB43311, OLE Study GB43374, is planned and will open subject to approval by local Institutional Review Boards or Ethics Committees (IRBs/ECs) and relevant health authorities. Patients who complete the study treatment period through the Week 52 treatment completion visit, including those patients receiving continued blinded treatment after Week 52, will be given the option to enter OLE Study GB43374 and receive treatment with open-label astegolimab, if eligible and provided that the OLE Study GB43374 is open in their respective country. The additional blinded treatment beyond Week 52 provides patients with the opportunity to remain in the study without a break in study treatment until OLE Study GB43374

becomes available. Patients who are ineligible for or choose not to enroll in OLE Study GB43374 will enter the safety follow-up period in this study (see Section 3.1.3).

Patients who discontinue study drug prematurely will not be eligible to participate in OLE Study GB43374 and will enter the safety follow-up period (see Section 3.1.3).

3.1.3 Safety Follow-up Period and Assessments after Study Treatment Discontinuation

Patients who complete the study treatment period through the Week 52 treatment completion visit (and enter the additional treatment period, if applicable, see Section 3.1.1) and do not enter OLE Study GB43374 will enter the safety follow-up period and undergo end of study assessments 12 weeks after the final dose of study drug.

Patients who discontinue study drug prematurely during the 52-week treatment period for the reasons listed in Section 4.6.1 should be asked to continue with all scheduled study assessments, with the exception of study drug administration and optional assessments (if applicable), through the end of the study. For these patients, telephone visits may replace certain in-clinic visits. Specific details are outlined in Appendix 1.

Patients who discontinue study drug prematurely during the 52-week treatment period for the reasons listed in Section 4.6.1 and are unwilling to complete the study assessments and patients who discontinue study drug during the additional treatment period should return to the clinic for a treatment discontinuation visit within 14 (+7) days of the event and will then enter the safety follow-up period, with end of study assessments 12 weeks after the final dose of study drug.

Patients who are unwilling to complete the safety follow-up period should return to the clinic for treatment discontinuation visit as soon as possible and no later than 30 days after their final dose (see Appendix 1 for additional details).

3.1.4 Independent Data Monitoring Committee

An iDMC will monitor safety data on an ongoing basis and conduct the planned interim analysis (see Section 6.9). 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 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 IRBs/ECs.

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

3.1.5 *Patient Input into Study Design*

A representative from the COPD Foundation was asked to provide feedback on the following aspects of the study:

- *Study design, endpoints, inclusion and exclusion criteria, schedule of activities, and patient-reported outcomes*
- *Recruitment and retention (e.g., inclusivity of underserved patient communities, potential recruitment challenges, possible retention challenges)*

This feedback was taken into consideration when developing the protocol.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined *based on the phase of enrollment. For the initial phase of the study, the end of study will be the date when the last patient of the initial phase (approximately 1290 patients) has their last visit.* The end of the study is expected to occur approximately 14 months after this last patient is enrolled. *For the second phase of the study (additional ~150 patients), the end of study will occur approximately 14 months after the last patient in this phase is enrolled.*

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient *in the initial phase* to the end of the study *in the second phase*, is expected to be approximately *49 months*.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Astegolimab Dose and Schedule

The two astegolimab dosing regimens, 476 mg Q2W and 476 mg Q4W, were selected on the basis of PK, pharmacodynamic (PD), and safety data from Phase I studies in healthy volunteers and efficacy and safety data from Phase II studies in patients with COPD, asthma, atopic dermatitis, and COVID-19 pneumonia. In addition, chemistry and manufacturing feasibility (pre-filled syringe vs. vial and syringe), clinical feasibility (number of injections), and other factors were taken into consideration for dose selection, including the change in dose from 490 mg (used in prior studies) to 476 mg in this study, which is expected to have a negligible effect on drug exposure.

In Phase II studies in patients with COPD and asthma, astegolimab dosed at 490 mg Q4W appeared to show a treatment benefit. In the Phase IIb dose-ranging Study GB39242 in patients with asthma, the rate reduction of asthma exacerbations

after 52 weeks of treatment was 43% for astegolimab 490 mg ($p=0.0049$). In the IIS Study GB40568 in patients with COPD, which was powered for a 40% reduction in annualized exacerbation rate, astegolimab 490 mg reduced the number of exacerbations by 22%, although this reduction was not statistically significant ($p= 0.195$). In Study GB39242, whereas there was lack of consistent and clear dose-response and exposure-response relationships for the primary endpoint (annual exacerbation rate ratio), positive dose-response and exposure-response trends were observed for FEV_1, suggesting that there could be additional clinical benefit from higher doses such as 476 mg Q2W.

In the Phase I studies in healthy volunteers, the highest single doses of astegolimab tested were 700 mg IV and 560 mg SC, and the highest multiple doses were 700 mg IV (Q4W for three doses) and 210 mg SC (Q2W for six doses). These doses were well tolerated, and no significant safety issues were identified. In addition, astegolimab 490 mg Q4W tested in patients with COPD, asthma, and atopic dermatitis, and 700 mg IV tested in patients with severe COVID-19 pneumonia were well tolerated and had safety profiles consistent with those observed in previous clinical studies.

The two dosing regimens to be tested in this COPD study (476 mg Q2W and 476 mg Q4W) are expected to have sufficient safety coverage, based on the no-observed-adverse-effect level of 300 mg/kg SC biweekly from the 6-month repeat-dose toxicity study and the simulated exposure levels at steady state for these dosing regimens. The simulated safety margins for area under the concentration–time curve (AUC) and maximum concentration (C_{max}) of 476 mg Q4W were 47- and 61-fold, respectively, and the simulated safety margins for AUC and C_{max} of 476 mg Q2W were 24- and 36-fold, respectively.

3.3.2 Rationale for Patient Population

Frequent exacerbations significantly impact symptoms, health-related quality of life, physical function, disease progression, healthcare utilization, and mortality in COPD (Anzueto 2010). Patients with COPD who have two or more moderate to severe exacerbations within a 12-month period are at the greatest continued risk of future exacerbations (Han 2017). Therefore, it is in this group of patients that the most benefit is expected from a reduction in exacerbations. History of prior exacerbations is a stronger predictor of future exacerbation risk than severity of airflow obstruction, inflammatory markers, and functional or clinical markers (Hurst 2010). While the frequency of exacerbations increases with severity of airflow obstruction, a significant proportion of patients with moderate airflow obstruction experience a high frequency of exacerbations (Decramer 2009). This study will therefore enroll patients with moderate to very severe airflow obstruction who have a history of frequent exacerbations (defined as an annual rate of two or more exacerbations).

3.3.3 Rationale for Control Group

The study will compare the efficacy, safety and pharmacokinetics of astegolimab in combination with SOC (defined in Section 4.3.2.2) compared with placebo in combination with SOC in patients with COPD. Treatment with SOC ensures that all patients receive therapy for COPD; the placebo control group takes into account safety, efficacy, and ethical considerations for studying the effects of astegolimab.

3.3.4 Rationale for Biomarker Assessments

COPD is a heterogeneous disease, and *IL33* and sST2 expression has been shown to vary among patients. Therefore, all patients may not be equally likely to benefit from treatment with astegolimab. Biomarker assessments, before and at various timepoints after treatment, will be used to provide evidence of the biologic activity of astegolimab in patients, identify biomarkers that may be predictive of response to astegolimab, define PK and/or PD relationships, advance the understanding of the mechanism of action of astegolimab in patients, support selection of a recommended dose regimen, and increase the knowledge and understanding of disease biology. Exploratory biomarker analysis may include, but will not be limited to, analysis of eosinophils, IL-33 pathway markers (e.g., sST2), and inflammatory mediators (e.g., fibrinogen and C-reactive protein).

A blood sample will be collected for DNA extraction to enable identification of specific germline mutations in *IL1RL* and *IL33* and other genes related to COPD that may be predictive of response to study drug, are associated with disease progression, or can increase the knowledge and understanding of disease biology.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.3.5 *Rationale for Additional Intensive PK Sampling and Airway Biomarker Substudy Enrollment*

Protocol GB43311 Version 4 has been amended to modify study conduct pertaining to Intensive PK sampling (Section 4.5.15) and the Airway Biomarker Substudy (Section 4.5.16), allowing for additional patient enrollment after full enrollment of the initial phase of the study where these assessments were optional. Patients enrolling in the second phase of the study are now required to participate in at least one of these assessments. These assessments were included in this protocol to further characterize the pharmacokinetic properties of astegolimab and to better understand the biology of

astegolimab in study participants. While exploratory, these assessments are important to better understand the pharmacokinetic properties of astegolimab and to collect further biomarker data to support future drug development.

All patients enrolled, regardless of phase, will be subject to the same conditions of the protocol (e.g., stopping rules, assessments and their timing, access to additional treatment period and OLE) except for additional assessments deemed mandatory for patients enrolled after the initial phase of the study is fully enrolled and the timing of interim and primary efficacy analyses (as described in Section 6).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately *1440 patients* with COPD and a history of frequent exacerbations will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 40–90 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Documented physician diagnosis of COPD made at least 12 months prior to screening
- History of frequent exacerbations, defined as having had two or more moderate or severe exacerbations occurring within a 12-month period in the 24 months prior to screening

  Exacerbations should have been treated with systemic corticosteroids and/or antibiotics.

  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 $\geq$3 days) with systemic corticosteroids (oral, IV, or IM) at a dose of $>$10 mg/day prednisolone equivalent and/or antibiotics. Prior use of antibiotics alone does not qualify as a moderate exacerbation, unless the use was specifically for the treatment of worsening symptoms of COPD.

  A severe COPD exacerbation is defined as new or increased COPD symptoms that lead to hospitalization (duration $>$24 hours) or lead to death.
- Post-bronchodilator FEV_1 $\geq$20 and $<$80% of predicted normal value at screening, as verified by over-reader
- Post-bronchodilator FEV_1/FVC $<$0.70 at screening, as verified by over-reader
- mMRC score $\geq$2 at screening

- Current smoker or former smoker with a minimum of 10 pack-year history (e.g., 20 cigarettes/day for 10 years)

  A former smoker is defined as meeting the criteria above but has not used inhaled tobacco products or inhaled marijuana within 6 months prior to screening, through use of cigarettes, cigars, electronic cigarettes, vaporizing devices, or pipe.

  Note that at screening, patients who meet the protocol definition of current smoker will receive smoking cessation counseling (see Section 4.5.6).

- History of one of the following combinations of optimized, stable, standard-of-care COPD maintenance therapy for at least 4 weeks prior to screening, with no anticipated changes in therapy prior to initiation of study drug and throughout the study:
  - Inhaled corticosteroid (ICS) plus long-acting beta-agonist (LABA)
  - Long-acting muscarinic antagonist (LAMA) plus LABA
  - ICS plus LAMA plus LABA
- Demonstrated ability to use and comply with electronic diary (eDiary) requirements, defined as completion of all questions on at least 5 out of 7 consecutive days within the 14 days after the screening visit

  Patients unable to demonstrate compliance with the eDiary within the first 2 weeks of screening will be screen failed. Patients will have the opportunity to demonstrate eDiary compliance if re-screened (see Section 4.5.13.1).

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 12 weeks after the final dose of astegolimab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate

methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 12 weeks after the final dose of astegolimab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

- For patients enrolling in the Airway Biomarker Substudy (at participating sites; see Section 4.5.16): ability to produce at least 1 mL of sputum spontaneously or via sputum induction at screening

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 12 weeks after the final dose of study drug.

  Women of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test on Day 1 prior to initiation of study drug.

- Current documented diagnosis of asthma according to the Global Initiative for Asthma guidelines or other accepted guidelines within 5 years prior to screening
- History of clinically significant pulmonary disease other than COPD (e.g., pulmonary fibrosis, sarcoidosis, chronic pulmonary embolism or primary pulmonary hypertension, alpha-1-antitrypsin deficiency)
- Clinically significant abnormalities requiring clinical follow-up as indicated by chest X-ray or chest CT scan performed within 6 months prior to screening

  Chest X-ray must be performed at screening if results from a chest X-ray or chest CT scan performed within 6 months prior to screening are not available.

- Presence of risk factors for aspiration pneumonia (e.g., neurologic disease such as uncontrolled epilepsy) in the opinion of the investigator
- History of long-term treatment with oxygen at >4.0 liters/minute

  While breathing supplemental oxygen, patient should demonstrate an oxyhemoglobin saturation of $\geq 89\%$.

- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the study drug

- Lung volume reduction surgery or procedure within 12 months prior to screening
- Participation in or planned participation in a new pulmonary rehabilitation program within 4 weeks prior to screening and throughout the study treatment period

  Patients who are in the maintenance phase of a rehabilitation program are eligible.
- History of lung transplant
- Occurrence of moderate or severe COPD exacerbation (as defined in Section 4.1.1), COVID-19, upper or lower respiratory infection, pneumonia, or hospitalization of $\geq$24 hours duration within 4 weeks prior to initiation of study drug
- Any prior treatment with astegolimab
- Treatment with oral, IV, or IM corticosteroids ($>$10 mg/day prednisolone equivalent) within 4 weeks prior to initiation of study drug
- Treatment with investigational therapy within 3 months or 5 drug-elimination half-lives (whichever is longer) prior to screening
- Treatment with a licensed biologic agent (e.g., omalizumab, dupilumab, and/or anti-IL-5 therapies) within 3 months or 5 drug-elimination half-lives (whichever is longer) prior to screening
- Initiation of a methylxanthine preparation, maintenance macrolide therapy, and/or PDE4 inhibitor within 4 weeks prior to screening
- Initiation of or change in non-biologic immunomodulatory or immunosuppressive therapy within 3 months prior to screening
- Treatment that is considered palliative (e.g., for life expectancy $<$12 months)
- Use of any of the following treatments within 4 weeks prior to screening, or any condition that is likely to require such treatment during the course of the study, unless the treatment is deemed acceptable by the investigator, in consultation with the Medical Monitor:
  - Treatment with immunoglobulin or blood products.
  - Treatment with any live or attenuated vaccine (including any approved, live SARS-CoV-2 vaccine) within 4 weeks prior to screening or during the screening period, or anticipated need for live, attenuated vaccine during the course of the study, unless the vaccine is deemed medically necessary and no inactivated vaccine alternatives are available.
- Administration of non-live SARS-CoV-2 vaccine (with full marketing authorization or temporary), including those delivered by non-replicating viral vectors, within 7 days prior to initiation of study drug
- Planned surgical intervention during the study
- Positive hepatitis C virus (HCV) antibody test result accompanied by a positive HCV RNA test at screening

- Unacceptable test results for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and total hepatitis B core antibody (HBcAb) at screening, defined as meeting either of the following criteria:
  - Positive HBsAg test at screening.
  - Negative HBsAg test at screening, with negative HBsAb test accompanied by positive total HBcAb test, followed by quantitative hepatitis B virus (HBV) DNA $\geq$20 IU/mL. Inability to perform HBV DNA test is exclusionary.

  Patients with a negative HBsAg test and positive HBsAb test are eligible.
- Known immunodeficiency including, but not limited to, HIV infection

  Where required by local regulations: Patients must have a negative HIV test result at screening or within 3 months prior to screening.
- Known evidence of active or untreated latent tuberculosis
- Substance abuse, as determined by the investigator, within 12 months prior to screening
- History of malignancy within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival rate $>$90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, or ductal carcinoma in situ
- Any other serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Unstable cardiac disease, myocardial infarction, or New York Heart Association Class III or IV heart failure within 12 months prior to screening
- History or presence (as verified by over-reader) of an abnormal ECG that is deemed clinically significant by the investigator, including complete left bundle branch block or second- or third-degree atrioventricular heart block
- QT interval corrected through use of Fridericia's formula (QTcF) (as verified by over-reader) $>$450 ms if patient is male or QTcF $>$470 ms if patient is female

  For male or female patients with QRS $>$120: QTcF $>$ 480 ms.
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, significant left ventricular hypertrophy with strain), or family history of sudden unexplained death or long QT syndrome

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 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.

4.2.2 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 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. Postbaseline 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) that are considered by the investigator or Sponsor to be related to an investigational medicinal product (IMP; defined in Section 4.3). 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.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are astegolimab and placebo. Standard-of-care COPD maintenance therapies (as specified in Section 4.3.2.2), having been used prior to screening and continued throughout the study, are considered non-investigational medicinal products (NIMPs). *Appendix 9 identifies all investigational, auxiliary, and non-investigational medicinal products for this study.*

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Astegolimab and Placebo

Astegolimab and placebo will be supplied by the Sponsor as a sterile liquid [redacted] For information on the astegolimab and placebo formulation, see the pharmacy manual and/or Astegolimab Investigator's Brochure.

4.3.1.2 Standard-of-Care COPD Maintenance Therapy

All patients must be on optimized, stable, standard-of-care COPD maintenance therapy for at least 4 weeks prior to screening, with no anticipated changes in therapy prior to initiation of study drug and throughout the study (see Section 4.3.2.2 for more details).

For information on the formulation and packaging of these treatments, see the local prescribing information.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Refer to the pharmacy manual for detailed instructions on drug preparation and administration.

At applicable sites, study drug may be administered by a trained nursing professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in mobile nursing (MN) visits.

Details on study drug administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.13.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

4.3.2.1 Astegolimab and Placebo

Study drug administration must occur after all other procedures have been completed at the visit, unless specifically indicated otherwise. Study drug will be administered by trained medical personnel.

Each dose of study drug (astegolimab or placebo) will be administered as two SC injections ([redacted]), with each injection administered on a different side of the abdomen (i.e., right or left). See the pharmacy manual for details on study drug preparation and administration.

All patients will be observed for at least 30 minutes after each dose and longer (approximately 60 minutes) in the event of an injection-site reaction, as determined by the investigator. If a patient develops any signs or symptoms to suggest a systemic hypersensitivity reaction or anaphylactic event, longer observation may be warranted in the opinion of the investigator.

There must be a minimum of 8 days between doses. In the event a dosing visit would occur within 8 days of a subsequent or previous dosing visit (e.g., due to an out-of-window visit), the study drug may not be administered. Instead, the next dose of study drug should be administered at the subsequent scheduled visit within the protocol-defined visit window to ensure that the 8-day minimum dosing interval is maintained.

Patients who are unable to tolerate study drug will discontinue treatment but will be asked to continue with study assessments. Study drug may be resumed after the events resolve, if the investigator determines that the event was not related to study drug and the investigator and Medical Monitor agree that it is appropriate for the patient to resume study drug. See Section 5.1.2 for specific guidelines for withholding or discontinuing study drug for patients who experience adverse events.

4.3.2.2 Standard-of-Care COPD Maintenance Therapy

All patients must be on one of the following combinations of optimized, stable, standard-of-care COPD maintenance therapy for at least 4 weeks prior to screening, with no anticipated changes in therapy prior to initiation of study drug and throughout the study:

- ICS plus long-acting beta-agonist (LABA)
- Long-acting muscarinic antagonist (LAMA) plus LABA
- ICS plus LAMA plus LABA

At screening, patients will be instructed on the proper technique recommended for administration of their ICS and inhaled bronchodilator therapy. From 4 weeks prior to screening through completion of the study, the doses of background COPD medications should remain stable. If changes to the background COPD medications are unavoidable, the patient may be switched to another brand or formulation that is

equivalent to the medication that the patient was receiving at the time of study entry. Proposed changes should be discussed with the Medical Monitor. All changes to a patient's background medications should be documented in the Concomitant Medications eCRF.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or mobile nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Astegolimab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Astegolimab

Patients may be eligible to receive astegolimab as part of an extension study offered by the Sponsor (Genentech, a member of the Roche Group), as described in Section 3.1.2.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

COPD-specific medications, biologics, and immunomodulatory drugs used by a patient from 6 months prior to initiation of study drug (Day 1) through the end of study/safety follow-up visit should be recorded on the Concomitant Medication eCRF. SARS-CoV-2 vaccines received by a patient from prior to screening through the end of the study/safety follow-up visit should be reported to the investigator and recorded on the Concomitant Medication eCRF. Other concomitant therapy, consisting of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 4 weeks prior to screening through the end of study/safety follow-up visit should be reported to the investigator and recorded on the Concomitant Medication eCRF.

4.4.1 Rescue Therapy

It is expected that patients will be using short-acting anti-cholinergic and/or short-acting beta-agonist therapy for acute COPD symptoms per existing treatment guidelines. Combination inhalers (e.g., albuterol/ipratropium) are permitted. Short-acting bronchodilators must be administered via the patient's prescribed inhaler or nebulizer.

Patients will record their use of short-acting rescue therapy in the eDiary (see Section 4.5.13.2 for details). Any short-acting bronchodilator that is prescribed as COPD rescue medication during the study should be documented in the Concomitant Medications eCRF. Bronchodilator treatment administered during an urgent health care visit or hospitalization should also be recorded in the Concomitant Medication eCRF.

4.4.2 Systemic Corticosteroids

Patients who require oral, IV, or IM corticosteroid treatment ($>$10 mg/day prednisolone equivalent) within 4 weeks prior to initiation of study drug will not be eligible for the study (see Section 4.1.2).

Chronic use (duration of therapy $\geq$2 weeks) of oral, IV, or IM corticosteroids ($>$10 mg/day prednisolone equivalent) is not permitted during the study treatment period, unless indicated for a COPD exacerbation event.

The use of oral, IV, or IM corticosteroids is permitted for acute patient management after initiation of study drug and should be documented on the Concomitant Medication eCRF. Documentation should include dose, total duration of therapy, and whether or not use is associated with a COPD exacerbation event. See Table 1 for additional details on restrictions for use of systemic corticosteroids.

4.4.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.4 COPD Therapy and Concomitant Therapy Restrictions

Restrictions regarding the use of COPD therapy and concomitant therapy are summarized in Table 1.

Table 1 COPD Therapy and Concomitant Therapy Restrictions

Therapy	Restrictions for Use	
	Prior to Study Treatment	During Study Treatment
One of the following SOC combinations: ICS + LABA LAMA + LABA ICS + LAMA + LABA	Regimen stable for at least 4 weeks prior to screening, with no anticipated changes in therapy prior to initiation of study drug	No changes during study treatment except as noted in Section 4.3.2.2
Non-biologic immunomodulatory or immunosuppressive therapy (e.g., methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine)	Regimen stable for at least 3 months prior to screening [a]	No anticipated changes during study treatment [a]
Systemic corticosteroids (oral, IV, or IM)	Doses of > 10 mg/day prednisolone equivalent prohibited within 4 weeks prior to initiation of study drug	Doses of > 10 mg/day prednisolone equivalent, with duration of therapy ≥ 2 weeks, prohibited during study treatment [e]
Astegolimab	Prohibited (any use) prior to study	—

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SOC = standard of care.

[a] Unless deemed acceptable in consultation with the Medical Monitor.

[b] Investigational SARS-CoV-2 vaccines (i.e., vaccines given as part of a clinical trial) are prohibited. Approved live-attenuated SARS-CoV-2 vaccines, if available, are subject to the live-attenuated vaccine restrictions.

[c] Patients who are in the maintenance phase of a rehabilitation program are eligible (see Section 4.1.1).

[d] Patients participating in a clinical trial that has not been unblinded should be assumed to have received active drug.

[e] Unless indicated for an acute COPD exacerbation (as defined in Section 4.5.7).

Table 1 COPD Therapy and Concomitant Therapy Restrictions (cont.)

Therapy	Restrictions for Use	
	Prior to Study Treatment	During Study Treatment
Methylxanthine preparations, maintenance macrolide therapy, and/or PDE4 inhibitors	Prohibited if initiated within 4 weeks prior to screening	Prohibited if initiated during study treatment
Licensed biologic agent (e.g., omalizumab, dupilumab, and/or anti-IL-5 therapies)	Prohibited within 3 months or 5 drug-elimination half-lives (whichever is longer) prior to screening	Prohibited during study treatment
Live-attenuated vaccines	Prohibited within 4 weeks prior to screening [a]	Prohibited during study treatment [a]
Non-live SARS-CoV-2 vaccines (with full marketing authorization or temporary) [b]	Prohibited within the 7 day period prior to initiation of study drug	Prohibited within the 7 day period prior to the treatment completion/discontinuation visit
Immunoglobulin or blood products	Prohibited within 4 weeks prior to screening [a]	Prohibited during study treatment [a]
Pulmonary rehabilitation	Initiation of or planned initiation in new pulmonary rehabilitation program prohibited within 4 weeks prior to screening [c]	Initiation of new pulmonary rehabilitation program prohibited during study treatment [c]
Any investigative therapy not described above (including investigational use of a formulation of an approved drug) [d]	Prohibited within 3 months or 5 drug-elimination half-lives (whichever is longer) prior to screening	Prohibited during study treatment

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SOC = standard of care.

[a] Unless deemed acceptable in consultation with the Medical Monitor.

[b] Investigational SARS-CoV-2 vaccines (i.e., vaccines given as part of a clinical trial) are prohibited. Approved live-attenuated SARS-CoV-2 vaccines, if available, are subject to the live-attenuated vaccine restrictions.

[c] Patients who are in the maintenance phase of a rehabilitation program are eligible (see Section 4.1.1).

[d] Patients participating in a clinical trial that has not been unblinded should be assumed to have received active drug.

[e] Unless indicated for an acute COPD exacerbation (as defined in Section 4.5.7).

4.4.5 Additional Restrictions

At study visits where fasting glucose and/or fasting lipids are measured (see Appendix 1), no food or fluids other than water will be allowed for approximately 8 hours prior to the visit and until after study laboratory samples are obtained.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for adverse events prior to each dose; dosing will occur only if the clinical assessment and available laboratory test values are acceptable.

At applicable sites, certain study assessments may be performed by an MN professional at the patient's home or another suitable location, to improve access and convenience for patients participating in the study. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, MN visits will be scheduled on specified visit days to allow for relevant assessments to be performed by the MN professional. The schedules of activities (Appendix 1 and Appendix 2) will specify the assessments that may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. The first re-screen may occur any time, starting the day after the patient's initial screen failure. A second re-screening opportunity is permitted, at minimum, 6 months after failing the first re-screen. Patients are not required to re-sign the Consent Form if they are re-screened within 28 days after previously signing the Consent Form. In the event the patient is re-screened, screening assessments should be repeated as follows:

- If patient is re-screened $\leq$ 28 days after the initial Informed Consent Form is signed, only the assessments that triggered screen failure need to be repeated.
- If patient is re-screened $>$ 28 days after the initial Informed Consent Form is signed, all screening assessments must be repeated, with the exception of the chest X-ray and collection of hepatitis serologies. Hepatitis B and C testing must be repeated only if re-screening occurs $>$ 3 months after the initial Informed Consent Form is signed. Chest X-ray must be repeated if results from a chest X-ray or chest CT scan performed within 6 months prior to re-screening are not available. Patients must re-sign the Informed Consent Form.

- If patient is re-screened for a second time (minimum 6 months after failing the first re-screen), all screening assessments must be repeated. Patients must re-sign the Informed Consent Form.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, reproductive status, smoking history, and use of alcohol will be recorded at baseline. In addition, COPD-specific medications, biologics, and immunomodulatory drugs used by the patient from 6 months prior to initiation of study drug (Day 1) will be recorded. All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 4 weeks prior to screening will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

A COPD-specific history including exacerbation history, detailed history of COPD medications in the 6 months prior to the initiation of study drug, and a patient-reported history of signs and symptoms of chronic bronchitis will be captured in the appropriate eCRF. Chronic bronchitis is defined as a chronic productive cough for at least 3 months in the year prior to screening; other causes of chronic cough (e.g., bronchiectasis) are excluded.

Demographic data, including age, sex, and self-reported race-/ethnicity, will be used to explore pharmacodynamic and safety effects.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Limited, symptom-directed physical examinations may be performed by an MN professional.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, peripheral oxygen saturation, and systolic and diastolic blood pressure, ideally while the patient is in a seated position after 5 minutes of rest, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital sign measurement may be performed by an MN professional.

4.5.5 Smoking History

At specified study visits, the patient will be asked about their smoking history. Any changes in smoking history since screening will be recorded in the appropriate eCRF.

Patients may discontinue smoking at any time during the study.

4.5.6 Smoking Cessation for Current Smokers

At screening, patients who are current smokers (as defined in Section 4.1.1) will receive smoking cessation counseling.

Patients will be reminded that smoking may accelerate the rate of lung function decline, worsen respiratory symptoms, increase the risk of lung cancer, and increase the risk of cardiovascular disease. Over time, smoking cessation may lead to a slower rate of lung function decline, improve respiratory symptoms, and reduce the risk of cardiovascular disease. Patients may be referred to their primary care physician or local services, as applicable, for further smoking cessation support.

4.5.7 COPD Exacerbation Assessment

At each study visit, an assessment will be conducted to determine if the patient experienced any protocol-defined acute COPD exacerbation since the previous study visit. In addition, at baseline and at specified visits, patients will be asked about their mask-wearing behavior. Any changes in mask-wearing behavior from baseline will be recorded in the appropriate eCRF.

An acute COPD exacerbation is defined as an exacerbation that meets the criteria for either moderate or severe exacerbation as follows:

- 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 $\geq$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.

An acute COPD exacerbation occurring $\leq$7 days after the final dose of systemic corticosteroids (oral, IM, or IV) and/or antibiotic therapy indicated for a previous exacerbation will be captured as a single exacerbation event.

Given that the annualized rate of COPD exacerbations is the primary endpoint in this study, a dedicated eCRF will be used to record information regarding protocol-defined acute exacerbation events. An acute COPD exacerbation must also be reported as an adverse event (or serious adverse event as applicable) as per Section 5.2. Sites should record all medications used for treatment of any COPD exacerbation in the appropriate eCRF.

4.5.8 Radiographic Assessments

A chest X-ray must be performed at screening to confirm the absence of any significant pulmonary disease other than COPD, unless results are available for chest X-ray or chest CT scan performed within 6 months of screening.

4.5.9 Five-Repetition Sit-to-Stand Test

The 5STS test will be conducted in line with instructions from the Short Physical Performance Battery tool (Guralnik et al. 1994). The test has been validated in patients with COPD (Jones et al. 2013). The 5STS assesses the time taken to stand up from a seated position five times, in as rapid succession as possible. The functional test relates strongly to lower limb function and frailty in patients with COPD; an inability to perform a single sit-to-stand or to complete five repeat sit-to-stands within 60 seconds denotes an inability to perform the test. Training on providing instructions and recording results will be provided.

4.5.10 Spirometry

Spirometry, including the procedure for bronchodilator testing, will be conducted as per the study pulmonary function testing manual, which is based on the American Thoracic Society (ATS) and European Respiratory Society (ERS) technical statement, “Standardization of Spirometry 2019 Update” (Graham et al. 2019). The manual will include information on equipment, procedures, patient instructions, and precautions. Standardized ATS- and ERS-compliant spirometric equipment, including software, will be dispensed to all sites. Training on equipment use, system calibration, and data storage and transfer will be provided.

Blinded over-readers will determine the acceptability of the data, including the graphic representations of the maneuvers, at screening to confirm eligibility and during the study. Calculations for the reproducibility of the acceptable maneuvers will be programmed.

Pre-bronchodilator spirometry and post-bronchodilator spirometry will be performed in the morning (prior to 1 p.m.) according to the schedule of assessments in Appendix 1. For safety reasons, consideration should be given to omitting spirometry if a patient is having an acute COPD exacerbation event (as defined in Section 4.5.7) at the time of the scheduled study visit.

4.5.10.1 Pre- Bronchodilator Spirometry

Pre-bronchodilator spirometry evaluations must be performed before use of bronchodilators. COPD therapies that may affect spirometry must be withheld until pre-bronchodilator spirometry measurements are completed. Patients must be made aware that bronchodilator use is prohibited within a specified window prior to each visit at which pre-bronchodilator spirometry is assessed, as follows:

- Twice-daily LABA and twice-daily LAMA: prohibited within 12 hours prior to spirometry
- Once-daily LABA and once-daily LAMA: prohibited within 24 hours prior to spirometry
- Short-acting β-agonist or short-acting muscarinic antagonist: prohibited within 4 hours prior to spirometry

If a patient inadvertently uses bronchodilators before pre-bronchodilator spirometry is assessed, the visit should not be rescheduled, and all other visit assessments should be performed as indicated in Appendix 1.

Pre-bronchodilator spirometry at screening that fails quality testing (as determined by the over-reader) should not be repeated if the post-bronchodilator spirometry maneuvers at screening are considered of acceptable and reproducible quality.

4.5.10.2 Post-Bronchodilator Spirometry

Maximal bronchodilation will be achieved via administration of either albuterol (90 μg metered dose) or salbutamol (100 μg metered dose), with or without a spacer device, up to a maximum of four inhalations. FEV_1 measurements should be recorded 20 to 30 minutes after bronchodilator use. For visits that require pre-bronchodilator spirometry, bronchodilator administration should be administered between 15–45 minutes after pre-bronchodilator spirometry.

4.5.11 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis. In the event of an unanticipated delay in central laboratory sample analysis, laboratory samples for safety (e.g., pregnancy test, hematology, chemistry panel) may be sent to the study site's local laboratory for analysis.

- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate, sodium, potassium, chloride, glucose, urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- HIV serology (where required by local regulations)
- HBV serology: HBsAg, HBsAb, and total HBcAb for all patients; HBV DNA for patients with negative HBsAg and HBsAb tests and a positive total HBcAb test

  For patients with $<$20 UI/mL HBV DNA at screening, the HBV DNA test will be repeated at Week 12 and Week 36. If the HBV DNA is $\geq$20 UI/mL at either of those timepoints, the Medical Monitor should be notified.

- HCV serology: HCV antibody for all patients; HCV RNA for patients with a positive HCV antibody test

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

- Fasting lipids: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
- Fasting glucose
- Hemoglobin A_{1c} (HbA_{1c})

The following samples will be sent to the Sponsor or a designee for analysis:

- Serum samples for astegolimab PK analysis
- Serum samples for astegolimab immunogenicity analysis
- Blood, serum, plasma samples for exploratory research on biomarkers

Exploratory biomarker research may include, but will not be limited to, the analysis of eosinophils, IL-33 pathway markers (e.g., sST2), inflammatory proteins (e.g., fibrinogen, C-reactive protein), and single nucleotide polymorphisms of selected genes (e.g., *IL1RL1*, *IL33* and other genes related to COPD). Research may involve extraction of DNA or RNA, analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Genomic research will be aimed at exploring inherited characteristics.

Blood and urine sample collection may be performed by an MN professional.

Screening blood samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.17) biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, serum, and plasma samples collected for biomarker research will be destroyed no later than 10 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.12 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedules of activities (Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as indicated. At screening, ECG recordings will be verified by an over-reader to determine patient eligibility.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes.

Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation, blood draws) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the central ECG laboratory and the data will be sent to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data. Clinically significant waveform changes or other clinically significant ECG abnormalities must be documented as adverse events on the Adverse Event eCRF (see Section 5.2.1). If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1.2.3. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.13 Clinical Outcome Assessments

The following patient-reported outcome (PRO) instruments will be completed to assess the treatment benefit and patient experience of astegolimab: SGRQ-C, mMRC, CAT, and EXACT.

4.5.13.1 Data Collection Methods for Clinical Outcome Assessments

The SGRQ-C, mMRC, and CAT will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1) and the EXACT will be self-administered at home on a daily basis. At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. The instruments will be translated as required into the local language.

PRO instruments will be completed through use of electronic devices provided by the Sponsor or through a secured website. The SGRQ-C, mMRC, and CAT will be completed via tablet device used at the clinic and the EXACT via take-home eDiary device. Both types of devices will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic devices/secured website and instructions for completing the instruments

electronically will be provided by the site staff. In cases where the electronic device cannot be used (e.g., the patient is unable to visit the site in person or because of device malfunction), the instruments may be administered via a secured web platform using the patient's own electronic device at home and/or using a computer at the clinic. Data collected via secured website will use technology platforms that will protect the patient's information and data according to local regulation and requirements. All data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

At screening, all patients will receive hands-on training in use of the eDiary, including review of the User Guide. Patients will also be instructed to contact the site if they have any questions about the use of the device during screening or at any time during the study. Compliance with required use of the eDiary, defined as completion of all questions on at least 5 of 7 consecutive days within the 14 days after the initial screening visit, must be demonstrated. Patients unable to demonstrate compliance with the eDiary within the first 2 weeks of screening will be screen failed. The patient will have the opportunity to demonstrate eDiary compliance if re-screened (see Section 4.5.1).

After randomization, weekly eDiary compliance, defined as completion of all questions on at least 4 out of 7 days each week, is required to optimize data quality and minimize the underestimation of symptom-defined events due to missing data.

Patients should be given the following instructions for completing PRO instruments at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 10 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.

- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.13.2 Description of Clinical Outcome Assessment Instruments

Saint George's Respiratory Questionnaire-COPD

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). The SGRQ-C consists of 40 questions within 3 domains: symptoms (7 items), activity (13 items), and impacts (20 items). Each response has a unique, empirically derived weight. A total score is also produced. Lower scores of the SGRQ-C indicate better health-related quality of life. The SGRQ-C has no specific recall period, with the exception of one item that assesses the frequency of chest trouble attacks during the past year. The SGRQ-C takes approximately 10 minutes to complete. A copy of the assessment is provided in Appendix 4.

Modified Medical Research Council Dyspnea Scale

The mMRC assesses activity-associated dyspnea via a single item that requires patients to select one of five statements best describing their level of breathlessness, with lower scores corresponding to less dyspnea impact. The mMRC has no specified recall period; it captures the patient's current status at the timepoint of administration. A copy of the scale is provided in Appendix 6.

COPD Assessment Test

The COPD Assessment Test (Jones et al. 2009) is a validated PRO that measures the impact of COPD on health status. The CAT 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. There is no specified recall period (questions are answered in reference to daily life); the questionnaire takes 1-2 minutes to complete. A copy of the assessment is provided in Appendix 7.

EXAcerbations of Chronic Pulmonary Disease Tool and Evaluating Respiratory Symptoms in COPD (EXACT) Questionnaire and Evaluating Respiratory Symptoms in COPD (E-RS:COPD) Subset

The 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). 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 three domains. The daily eDiary entry, including the EXACT plus the short-acting rescue medication question (see below), takes approximately 5 minutes to complete. Patients are asked to complete the diary every evening before going to bed. A copy of the EXACT assessment is provided in Appendix 5.

Short-Acting Rescue Medication

A single item asking about rescue inhaler use will be administered together with the EXACT as part of the daily eDiary. A copy of the assessment is provided in Appendix 5.

4.5.14 Optional Physical Activity Monitoring (Consenting Patients at Participating Sites)

Approximately 150 patients at participating sites will wear a physical activity monitor to assess changes in patient physical activity such as daily step count or time in moderate-to-vigorous physical activity. Physical activity is an objective, real-world measure influenced by underlying symptoms, patient motivation, and functional capacity.

The monitor will be worn for four periods of up to 2 weeks each (minimum of 1 week) during the study (see Appendix 1). Patients should be encouraged to wear the monitor as much as possible on the same location of the body during the monitoring period, taking off the monitor only when necessary to recharge. Training and instructions on dispensing the device, information for patients, and data collection will be provided.

The Informed Consent Form will contain a separate section that addresses the optional physical activity monitoring. A separate, specific signature will be required to document a patient's agreement to undergo optional physical activity monitoring *in the initial phase of the study*. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date of consent, by completing the appropriate eCRF.

4.5.15 Intensive Pharmacokinetic Sampling (Consenting Patients at Participating Sites)

Approximately 240 patients at participating sites (approximately 160 patients receiving astegolimab) will undergo collection of additional blood samples at prespecified timepoints (see Appendix 3) to inform the pharmacokinetic properties of astegolimab in relation to efficacy and safety endpoints in patients with COPD.

The Informed Consent Form will contain a separate section that addresses the intensive PK sampling. A separate, specific signature will be required to document a patient's agreement to undergo collection of additional blood samples. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date of consent, by completing the appropriate eCRF. *After complete*

enrollment of the initial phase of the study (~1290 patients), patients will be required to participate in at least one of the following assessments: (a) intensive PK sampling (Section 4.5.15) and (b) the Airway Biomarker Substudy (Section 4.5.16). Patients enrolled in the second phase of the study who do not complete at least one of these activities may be replaced.

Samples will be sent to the Sponsor or a designee for analysis. Samples may be used for PK assay development as described in Section 4.5.11. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.11 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from PK analyses.

4.5.16 Assessments Specific to Airway Biomarker Substudy (Consenting Patients at Participating Sites)

Approximately 100 consenting patients at participating sites will undergo additional assessments in an Airway Biomarker Substudy that is designed to further characterize the airways and exacerbations experienced by study participants. Substudy-specific assessments consist of blood, serum, plasma, sputum, and nasosorption sample collection, chest HRCT, pre-bronchodilator spirometry, and total body plethysmography at specified timepoints during the 52-week treatment period (see Appendix 1).

Given that repeat sputum sampling will be required for the Airway Biomarker Substudy, participating patients must be able to produce 1 mL of sputum spontaneously or via sputum induction at screening (see Section 4.1.1). Instructions and training for inducing sputum and collecting nasosorption samples will be provided.

Patients enrolled in the Airway Biomarker Substudy who experience an acute COPD exacerbation during the study will be asked to return to the clinic for an exacerbation visit to undergo assessments as detailed in the schedule of activities (Appendix 1). The exacerbation visit assessments should occur before commencing treatment for the exacerbation, whenever possible.

The Informed Consent Form will contain a separate section that addresses the Airway Biomarker Substudy. At screening, a separate, specific signature will be required to document a patient's agreement to undergo the substudy assessments. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date of consent, by completing the appropriate eCRF. *After complete enrollment of the initial phase of the study (~1290 patients), patients will be required to participate in at least one of the following assessments: (a) intensive PK sampling (Section 4.5.15) and (b) the Airway Biomarker Substudy (Section 4.5.16). Patients enrolled in the second phase of the study who do not complete at least one of these activities may be replaced.*

Samples will be sent to the Sponsor or a designee for analysis. Samples may be used for exploratory biomarker research as described in Section 4.5.11. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.17), blood, serum, plasma, sputum, and nasosorption samples collected for biomarker research will be destroyed no later than 10 years after the final Clinical Study Report has been completed.

Refer to Section 4.5.11 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.17 Optional Samples for Research Biosample

4.5.17.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.17.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.17) will not be applicable at that site.

4.5.17.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to astegolimab or COPD or drug safety:

- Blood samples collected at randomization
- Leftover blood, plasma, serum, sputum, and nasosorption samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.17.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.17.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.17.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.17.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)

Patients who discontinue study treatment prematurely should be asked to continue with all scheduled study assessments (see Section 3.1.3 for additional details). Any patient that discontinues study treatment prematurely will not be eligible to participate in OLE Study GB43374 (see Section 3.1.2).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Refer to Section 3.1.3 and the schedules of activities (Appendix 1 and Appendix 2) for details on follow-up assessments to be performed for patients who permanently discontinue study treatment. If a patient requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Any patient that the investigator or Sponsor considers lost to follow-up

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Astegolimab is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with astegolimab in seven completed Phase I and Phase II studies, in healthy volunteers and patients with asthma, atopic dermatitis, COPD, and COVID-19 pneumonia (see Section 1.2.3, and ongoing review of this Phase II study, GB43311). As of the data cutoff of 8 March 2022, a total of approximately 583 patients and 109 healthy subjects have been exposed to at least one dose of astegolimab in the completed studies. The anticipated important safety risks for

astegolimab are outlined below. Please refer to the Astegolimab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Astegolimab

5.1.1.1 Identified Risks

No risks have yet been identified for astegolimab.

5.1.1.2 Potential Risks

Adverse Effects Related to Immunogenicity

Administration of astegolimab, a protein therapeutic, may lead to the development of anti-astegolimab antibodies, which could lead to adverse events and/or decreased exposure.

To monitor ADA development in ongoing studies, serum samples will be collected from patients at protocol-defined intervals. Patients who test positive for antibodies and have clinical sequelae that are considered potentially related to an ADA response may also be asked to return for additional follow-up testing.

For details about immunogenicity rates and associated adverse events, refer to the Astegolimab Investigator's Brochure.

Hypersensitivity Reactions and Anaphylaxis/Hypersensitivity-Like Reactions

Hypersensitivity reactions and anaphylaxis have been described with SC administration of monoclonal antibodies (Corominas et al. 2014). Signs and symptoms may include acute onset (minutes to several hours) of one or more of the following: respiratory compromise, reduced blood pressure, skin-mucosal involvement, or gastrointestinal symptoms (Sampson et al. 2006). The potential for hypersensitivity to astegolimab in humans is unknown. However, no allergic reactions occurred after a single IV or SC dose of astegolimab in the three completed Phase I studies. In patients receiving astegolimab in the completed Phase II studies, one moderate hypersensitivity event was reported.

As with any large-molecule therapeutic, administration of astegolimab may result in systemic reactions. Systemic reactions to large-molecule therapeutics can be IgE- or non-IgE– mediated or due to the release of cytokines. Reactions are generally characterized by signs and symptoms such as skin rash, urticaria, pruritus, local or

diffuse erythema, angioedema, fever, chills, cough, dyspnea, wheezing, bronchospasm, nausea, vomiting, diaphoresis, chest pain, tachycardia or bradycardia, and/or hypotension, which can be severe or life threatening. Effects typically occur during or within several hours after drug administration, but they may be delayed.

Patients with a history of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of astegolimab are excluded from the study.

Refer to the Astegolimab Investigator's Brochure for details about reports of adverse events of hypersensitivity reactions and anaphylaxis/hypersensitivity-like reactions.

Injection-Site Reactions

Injection-site reactions have been described with SC administration of monoclonal antibodies (Corominas et al. 2014). Signs and symptoms may include pain, itching, erythema, and swelling at the injection site. The reaction may be immediate, although it usually appears within 24–48 hours, with variable incidence according to the drug administered.

No clinically significant injection-site reactions associated with astegolimab were observed following single or repeat doses in cynomolgus monkeys or healthy volunteers in the Phase I studies. In the Phase IIb study GB39242, injection-site reactions were the most common drug-related adverse event and occurred more frequently in the three astegolimab-treated groups (ranging from 4.9 to 7.9% of patients) compared with placebo (0.8% of patients). All injection-site reactions were non-serious and mild or moderate in intensity, but led to study drug withdrawal in 3 patients.

During the study, all injection-site events should be accurately reported on the appropriate eCRF.

Refer to the Astegolimab Investigator's Brochure for details on injection-site reactions.

Infection

The intended mechanism of action of astegolimab suggests inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of a decrease in the protective response to infection, particularly helminthic infections (Molofsky et al. 2015). However, as described in the Astegolimab Investigator's Brochure, a lack of significant differences in levels of exploratory biomarkers fractional exhaled nitric oxide (reflecting airway IL-4/IL-13 activity) and serum IL-5 between patients treated with astegolimab and those treated with placebo in Study GB39242 in patients with asthma may reflect a limited effect on Type 2 inflammation.

In the three completed Phase I studies, no adverse events of infection related to study treatment were reported. During the treatment period in the Phase IIb Study GB39242, 427 events of infection were reported by 233 patients (46.4%) overall. A comparable

number of patients reported an event of infection across all treatment groups. The most frequently reported infection (≥ 10% incidence) was nasopharyngitis, reported by 64 patients (12.7%) across all treatment groups. None of the infections were considered related to study treatment or led to study treatment discontinuation.

All study participants will be monitored for signs and symptoms suggestive of infection by collection of vital signs, clinical laboratory tests, and adverse events.

Refer to the Astegolimab Investigator's Brochure for details about infections related to study treatment.

Exacerbation of Cardiovascular Disease

Published studies involving mouse models of cardiovascular disease or in vitro culture systems describe potential cardioprotective and atheroprotective roles of the IL-33/ST2 axis (Sanada et al. 2007; Miller et al. 2008; Seki et al. 2009; McLaren et al. 2010; Wasserman et al. 2012). However, the translatability of these findings remains uncertain. In addition, studies with conflicting data exist (Demyanets et al. 2011; Abston et al. 2012; Martin et al. 2015). In nonclinical toxicology and safety pharmacology studies with cynomolgus monkeys, including a 28-day and 6-month repeat-dose toxicology study as well as a single-dose cardiovascular safety study in telemetrized animals, no biologically significant changes were exhibited by astegolimab.

Evidence has shown that the sST2 receptor is a prognostic biomarker of cardiovascular disease outcome (Sabatine et al. 2008; Shah et al. 2009; Weir et al. 2010). Although published findings suggest a possible risk of exacerbation of existing cardiovascular disease in humans, there are no identified cardiovascular risks associated with inhibiting the IL-33/ST2 axis in humans.

In the three completed Phase I studies, no clinically significant treatment-related changes that either required new treatment or led to study or treatment discontinuation have been noted with vital signs, ECG assessments, physical exam, or other parameters that may be related to cardiovascular risk, such as HbA_{1c}, fasting glucose, and lipids. In the completed Phase II studies, none of the potential MACE were considered related to study drug or led to discontinuation of treatment, and all events were resolved.

Patients with active or unstable recent cardiovascular disease are excluded from the study. Baseline cardiovascular risk factors will be characterized via HbA_{1c}, fasting glucose, and lipid panels. Cardiac safety will be evaluated with monitoring of vital signs, ECG assessments, and the collection of relevant adverse events.

Refer to the Astegolimab Investigator's Brochure for details on the nonclinical and clinical experience associated with the potential risk of cardiovascular disease.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Treatment Interruption

Study treatment may be temporarily suspended in patients who experience treatment-emergent adverse events considered to be related to study drug. If study drug has been withheld for more than two consecutive scheduled doses because of an ongoing adverse event, the patient should be discontinued from study treatment, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Study treatment may be suspended for reasons other than adverse events (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.2.2 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 2. Additional guidelines are provided in the subsections below.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken
Hepatic Event	
ALT or AST increase that meets Hy's Law criteria (see Section 5.3.5.8): ALT or AST $>3\times$ULN in combination with TBILI $>2\times$ULN or clinical jaundice and having ruled out other medical sequelae to explain the combination of increased aminotransferase and serum TBILI.	• Discontinue study drug.
If abnormal liver function values, but the criteria for Hy's Law are not met: ALT or AST increase that meets at least one of the following criteria: • $>8\times$ULN • $>5\times$ULN for ≥ 2 weeks • $>3\times$ULN with clinical signs or symptoms that are consistent with hepatitis (e.g., right upper quadrant pain or tenderness, fever, nausea, vomiting, jaundice)	• Withhold study drug. • Study drug may be resumed if an alternative cause is identified and laboratory values have resolved to those at Day 1. • If signs or symptoms recur, permanently discontinue study drug.
If abnormal liver function values, but the criteria for Hy's Law are not met: TBILI $>3\times$ULN	• Consider withholding study drug. • Study drug may be resumed if an alternative cause is identified and laboratory values have resolved to those at Day 1. • If signs or symptoms recur, permanently discontinue study drug.
ALP $>3\times$ULN	• Consider withholding study drug. • Study drug may be resumed if an alternative cause is identified and laboratory values have resolved to those at Day 1. • If signs or symptoms recur, permanently discontinue study drug.
Cardiac Event	
Major adverse cardiovascular event	• Consider study drug interruption or discontinuation as per investigator judgment, based on the severity and nature of the MACE. [a] • Report event as an AESI (see Section 5.2.3).

AESI = adverse event of special interest; MACE = major adverse cardiovascular event; TBILI = total bilirubin; ULN = upper limit of normal.

[a] Refer to Section 5.2.3 for examples of events that qualify as major adverse cardiovascular events.

5.1.2.3 Management of Increases in QT Interval

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements >30 minutes apart) QTcF that is >500 ms and >60 ms longer than the baseline value
- Sustained absolute QTcF that is >515 ms (or >530 ms for patients with a ventricularly paced rhythm)
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval (e.g., azithromycin). Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients.

In rare circumstances, it may be acceptable to resume study drug, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

5.1.2.4 Anaphylaxis

Anaphylaxis should be promptly assessed and treated per local standard of care. For current guidelines, refer to Campbell et al. 2014:

https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Anaphylaxis-Practice-Parameter-2014.pdf

In accordance with current guidelines, the measurement of tryptase (serum or plasma) and histamine (plasma) levels should be considered to support a diagnosis of anaphylaxis, although clinicians should treat anaphylaxis regardless of the availability of the results of these tests.

During the study, all anaphylaxis events should be accurately reported on the appropriate eCRF.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, v2.1; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- MACE, including death due to cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke or transient ischemic attack, unstable angina, or cardiac chest pain requiring hospitalization, coronary revascularization, and congestive heart failure requiring hospitalization
- Anaphylaxis, anaphylactoid, and hypersensitivity reactions

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, including for all patients who discontinue study drug prematurely, all adverse events will be reported until 12 weeks after the final dose of study drug or until the last study visit, whichever is later.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The investigator will use the DAIDS toxicity grading scale (HHS 2017), with slight modifications for clarity and for alignment with internal practices (see Appendix 8) for assessing the severity of each adverse event reported during the study. The investigator will use the grading scale in Table 3 for assessing the severity of adverse events that are not specifically listed in the DAIDS toxicity grading scale.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in DAIDS Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

DAIDS = Division of AIDS.

Notes: Developed by the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4.

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction" or "anaphylactic reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated eCRF. If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated eCRF for injection reactions.

5.3.5.2 Major Adverse Cardiac Events

MACE (as defined in Section 5.2.3) should be recorded on the Adverse Event eCRF. Associated details should be recorded on the appropriate MACE eCRF.

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is

subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of COPD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of chronic obstructive pulmonary disease, "chronic obstructive pulmonary disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of COPD

Medical occurrences or symptoms of deterioration that are anticipated as part of COPD should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of COPD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of chronic obstructive pulmonary disease").

All acute exacerbations of COPD should be documented as an adverse event or serious adverse event, where applicable. Given that acute exacerbations of COPD are the primary endpoint for this study, a dedicated eCRF will be used to record additional information regarding COPD exacerbations (see Section 4.5.7).

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.13 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For astegolimab (or placebo), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with astegolimab (or placebo), regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug administered, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.14 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met (see Section 5.2.1) and, if so, will report the event on the Adverse Event eCRF.

5.3.5.15 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. These events should be reported immediately (i.e., no more than 24 hours after learning of the event) on the Adverse Event eCRF and the report submitted via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, including for patients who discontinue study drug prematurely, serious adverse events and adverse events of special interest will be reported until 12 weeks after the final dose of study drug or until the last study visit, whichever is later. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 12 weeks after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 12 weeks after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 12 weeks after the final dose of study drug. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 12 weeks after the final dose of study drug, see Section 5.3.1), if the event is believed to be related to prior exposure to study drug. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Astegolimab	Astegolimab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain serious adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting to applicable health authorities. These anticipated events include, but are not limited to, the following:

- COPD exacerbations

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Efficacy analyses will be conducted on the modified intent-to-treat (mITT) population. The mITT population is defined as all patients randomized in the study *in the initial study phase (approximately 1290 patients enrolled)* who received at least one dose of study drug, with patients grouped according to the treatment assigned at randomization.

Safety analyses will be conducted for the safety population, which consists of patients who received at least one dose of study drug *in the initial study phase (approximately 1290 patients enrolled),* with patients grouped according to the treatment received.

Patients enrolled in the second phase of the study after the last patient visit during the 52-week treatment period in the initial study phase will be used for exploratory analyses.

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

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 annualized exacerbation rate (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.

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 phase.

Given the continued impact of COVID-19 pandemic on COPD exacerbation rate, sample size re-estimation may be considered during the study.

6.2 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.

6.3 SUMMARIES OF DEMOGRAPHIC 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.

6.4 EFFICACY ANALYSES

Efficacy analyses will be conducted on the mITT population, consisting of all patients randomized in the study *in the initial study phase (n=1290)* who received at least one dose of study drug, with patients grouped according to the treatment assigned at randomization.

Comparison of efficacy 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

Sensitivity analyses to evaluate the robustness of results of the primary efficacy endpoint may be conducted and will be described in the SAP.

Details on analysis methods, sensitivity analyses, hypothesis testing, and type I error control across treatment groups will be specified in the SAP.

Unless otherwise noted, analyses of efficacy outcome measures will be adjusted by the stratification factors smoking status at screening (former smoker vs. current smoker) and region.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo on the basis of the following 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 $\geq$ 3 days) with systemic corticosteroids (oral, IV, or intramuscular [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.

The AER will be estimated as the total number of COPD exacerbations observed over the treatment period divided by the total patient-years at risk. For each individual patient, years at risk will be derived as the number of days from the date of randomization to the date of treatment completion or discontinuation, divided by 365.25 days. Poisson regression with overdispersion will be used to assess the treatment effect on AER. The regression model will be adjusted for baseline covariates, as described in Section 6.4. In addition, a patient's time at risk, as defined above, will be used as an offset item in the model.

Further analysis details on the primary endpoint analysis will be specified in the SAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study are as follows:

- Time to first moderate or severe COPD exacerbation during the 52-week treatment period
- Absolute change from baseline in HRQoL at Week 52, as assessed through the SGRQ-C total score
- Proportion of patients with improvement in HRQoL, defined as a decrease from baseline of $\geq$ 4 points in SGRQ-C total score, at Week 52
- 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
- Annualized rate of severe COPD exacerbations over the 52-week treatment period
- Absolute change from baseline in 5STS time at Week 52

The secondary endpoints will be analyzed in the mITT population. Full details of analysis methods, sensitivity analyses, hypothesis testing, and type I error control will be described in the SAP.

6.4.3 Exploratory Efficacy Endpoints

Analysis of exploratory efficacy endpoints will be described in the SAP as appropriate.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug *in the initial study phase,* with patients grouped according to treatment received. *Safety analysis of patients enrolled in the second study phase is described in Section 6.10.*

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

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to the DAIDS Table v2.1 (see Appendix 8). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, adverse events leading to discontinuation from study treatment, adverse events leading to discontinuation from study, and treatment-emergent adverse events 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 during. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign, and ECGs will be summarized by appropriate descriptive statistics by treatment groups.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters (e.g., AUC, time to maximum concentration [t_{max}], C_{max}, half-life), with patients grouped according to treatment received.

Individual and mean serum astegolimab concentration versus time data will be tabulated and plotted by dose level. The serum pharmacokinetics of astegolimab will be summarized by estimating total exposure (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 (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Inter-patient variability and drug accumulation will be evaluated. Assessment of protein binding will be performed on predose samples. Calculation of urine PK parameters (fractional excretion, renal clearance) will be performed.

For PK assessment, the concentrations of astegolimab at each PK sampling timepoint will be listed and summarized by descriptive summary statistics including means, geometric means, ranges, standard deviations, and coefficients of variation. Individual and mean concentration versus time data will be plotted. 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-PD relationship may be explored as appropriate.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one postbaseline 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 (postbaseline incidence) will be summarized by treatment group. When determining postbaseline 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.

6.8 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.

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 patients derives enhanced clinical benefit from astegolimab. Predictive biomarker candidates include, but are not limited to, germline mutations in *IL1RL1*.

PD biomarkers (e.g., 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.

Further details related to biomarker analyses will be described in the SAP.

6.9 INTERIM ANALYSIS FOR FUTILITY

An interim analysis for futility will be conducted by the iDMC after approximately 210 patients *in the initial study phase* have experienced at least one moderate to severe exacerbation event in the study. Detailed criteria for iDMC recommendations will be specified in the iDMC charter.

Further details on the rationale, timing, and statistical details of the analysis will be documented in the SAP. The SAP will be submitted to the relevant health authorities prior to the conduct of the interim analysis.

6.10 *SUBSTUDY ANALYSIS*

Additional analyses will be performed on patients enrolled in the second phase of the study where participation in at least one of the following assessments is required: (a) intensive PK sampling and (b) the Airway Biomarker Substudy. Results from the second study phase may be summarized in a separate CSR once patients have completed this study phase.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of electronic devices provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Electronic devices will be used to capture PRO data. They are designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays,

patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data, Informed Consent Forms, laboratory test results, medication inventory records, and images, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. *In addition, data may be disseminated as described in Section 9.6.*

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche Group, is the sponsor of this study. A CRO may provide clinical operations oversight as specified in the study management plans. The Sponsor will provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. The Sponsor may provide clinical operations management, data management, and medical monitoring.

An EDC system will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into the study, and manage site drug supply. Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.11. Accredited local laboratories will be used In the event of an unanticipated delay in central laboratory sample analysis.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional

monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Abston ED, Baron JG, Cihakova D, et al. IL-33 independently induces eosinophilic pericarditis and cardiac dilation: ST2 improves cardiac function. Circ Heart Fail 2012;5:366–75.

AbuDagga A, Sun SX, Tan H, et al. Healthcare utilization and costs among chronic bronchitis patients treated with maintenance medications from a US managed care population. J Med Econ 2013;16:421–9.

Anzueto A. Impact of exacerbations on COPD. Eur Respri Rev 2010;19:113–18.

Byers DE, Alexander-Brett J, Patel AC, et al. Long-term IL-33-producing epithelial progenitor cells in chronic obstructive lung disease. J Clin Invest 2013;123:3967–82.

Campbell RL, Li JTC, Nicklas RA, et al. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol 2014;113:599–608.

Cazzola M, Ora J, Puxeddu E. Dual bronchodilation and exacerbations of COPD. J Thorac Dis 2016;8:2383–6.

Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from TORCH study. Am J Respir Crit Care Med 2008;178:332–8.

Corominas M, Gastaminza G, Lobera T. Hypersensitivity reactions to biological drugs. J Investig Allergol Clin Immunol 2014;24:212.

Decramer M, Celli B, Kesten S, et al. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet 2009;374:1171–8.

Demyanets S, Konya V, Kastl SP, et al. Interleukin-33 induces expression of adhesion molecules and inflammatory activation in human endothelial cells and in human atherosclerotic plaques. Arterioscler Thromb Vasc Biol 2011;31:2080–89.

Diette GB, Dalal AA, D'Souza AO, et al. Treatment patterns of chronic obstructive pulmonary disease in employed adults in the United States. Int J Chron Obstruct Pulmon Dis 2015;415–22.

[GOLD] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2021 report. 2021 [cited 11 February 2021]. Available from: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf.

Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019;200:e70–e88.

Guralnik JM, Simonsick EM, Ferrucci L. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–94.

Halpin DMG, Decramer M, Celli B, et al. Exacerbation frequency and course of COPD. Int J Chron Obstruct Pulmon Dis 2012;7:653–61.

Han MK, Quibrera PM, Carretta EE, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. Lancet Respir Med 2017;5:619–26.

Hayakawa H, Hayakawa M, Kume A, et al. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. J Biol Chem 2007;282:26369–380.

Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004;350:2645–53.

[HHS] U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1 [resource on the Internet]. 2017 [cited: 12 July 2021]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128–38.

Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34:648–54.

Jones SE, Kon SSC, Canavan JL, et al. The five-repetition sit-to-stand test as a functional outcome measure in COPD. Thorax 2013;68:1015–20.

Kearley J, Silver JS, Sanden C, et al. Cigarette smoke silences innate lymphoid cell function and facilitates an exacerbated type I interleukin-33-dependent response to infection. Immunity 2015;42:566–79.

Landis SH, Muellerova H, Mannino DM, et al. Continuing to Confront COPD International Patient Survey: methods, COPD prevalence, and disease burden in 2012-2013. Int J Chron Obstruct Pulmon Dis 2014;9:597–611.

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;15:124.

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;13:965–75.

Liew FY, Girard J-P, Turnquist HR. Interleukin-33 in health and disease. Nat Rev Immunol 2016; 16:676–89.

Louten J, Rankin AL, Li Y, et al. Endogenous IL-33 enhances Th2 cytokine production and T-cell responses during allergic airway inflammation. Int Immunol 2011;23:307–15.

Martin P, Palmer G, Rodriquez E, et al. Atherosclerosis severity is not affected by a deficiency in IL-33/ST2 signaling. Immun Inflamm Dis 2015;3:239–46.

McLaren JE, Michael DR, Salter RC, et al. IL-33 reduces macrophage foam cell formation. J Immunol 2010;185:1222–29.

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;132:456–63.

Miller AM, Xu D, Asquith DL, et al. IL-33 reduces the development of atherosclerosis. J Exp Med 2008;205:339–46.

Miravitlles M, Ferrer M, Pont A, et al. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. Thorax 2004;59:387–95.

Molofsky AB, Savage AK, Locksley RM. Interleukin-33 in tissue homeostasis, injury, and inflammation. Immunity 2015;42:1005–19.

Nabe T. Interleukin (IL)-33: new therapeutic target for atopic diseases. J Pharmacol Sci 2014;126:85–91.

Patalano F, Banerji D, D'Andrea PD, et al. Addressing unmet needs in the treatment of COPD. Eur Respir Rev 2014;23:333–44.

Ravanetti L, Dijkhuis A, Dekker T. IL-33 drives influenza-induced asthma exacerbations by halting innate and adaptive antiviral immunity; J Allergy Clin Immunol 2019;143:1355–70.

Sabatine MS, Morrow, DA, Higgins LJ, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation 2008;117:1936–44.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391–7.

Sanada S, Hakuno D, Higgins LJ, et al. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 2007;117:1538–49.

Scanlon ST, McKenzie AN. Type 2 innate lymphoid cells: new players in asthma and allergy. Curr Opin Immunol 2012;24:707–12.

Seki K, Sanada S, Kudinova AY, et al. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. Circ Heart Fail 2009;2:684–91.

Shah RV, Chen-Tournoux AA, Picard MH, et al. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. Circ Heart Fail 2009;2:311–19.

Sims JE, Smith DE. The IL-1 family: regulators of immunity. Nat Rev Immunol 2010;10:89–102.

Solem CT, Sun SX, Sudharshan L, et al. Exacerbation-related impairment of quality of life and work productivity in severe and very severe chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2013;8:641–52.

Wasserman A, Ben-Shoshan J, Entin-Meer M, et al. Interleukin-33 augments Treg cell levels: a flaw mechanism in atherosclerosis. Isr Med Assoc J 2012;14:620–23.

Weir RA, Miller AM, Murphy GEJ, et al. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. J Am Coll Cardiol 2010;55:243–50.

Werder RB, Zhang V, Lynch JP. Chronic IL-33 expression predisposes to virus-induced asthma exacerbations by increasing type 2 inflammation and dampening antiviral immunity. J Allergy Clin Immunol 2018;141:1607–19.

[WHO] World Health Organization. Burden of COPD [resource on the Internet]. 2021 [cited 30 March 2021]. Available from: https://www.who.int/respiratory/copd/burden/en.

[WHO] World Health Organization. The top 10 causes of death the top ten causes of death [resource on the Internet]. 2020 [cited 30 March 2021]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

Appendix 1
Schedule of Activities

	Screen [a]	Treatment Period									Treat Compl/ Disc [b, c]	Add Treat Period [c]	EOS/ Safety Follow-Up [d]	EV [e]
Visit (V)	V1	V2 (Day 1)	V3—V7 [f, g, h] (every 2 wks)	V8	V9—V13 [f, g, h] (every 2 wks)	V14	V15—V19 [f, g, h] (every 2 wks)	V20	V21—26 [f, g, h] (every 2 wks)	V27 [g]	V28		V29	
Week	−4 to 0	0	2—10	12	14—22	24	26—34	36	38—48	50	52		62	
(Window)			(±3 days)										(±7 days)	
Informed consent	x [i]											See Appendix 2		
Demographic data	x													
Medical history and baseline conditions	x													
Smoking history	x	x		x		x		x			x		x	
Smoking cessation counseling [j]	x													
COPD exacerbation assessment		x [k]	x	x [k]	x	x [k]	x	x [k]	x	x	x [k]		x	x
SGRQ-C [l]		x		x		x		x			x			
mMRC [l]	x	x				x					x			
CAT [l]		x									x			
Daily eDiary [m]	x [m]	→	→	→	→	→	→	→	→	→	x			
Vital signs [n]	x	x	x	x	x	x	x	x	x	x	x		x	x

Appendix 1: Schedule of Activities

	Screen [a]	Treatment Period										Add Treat Period [c]	EOS/ Safety Follow-Up [d]	EV [e]
											Treat Compl/ Disc [b, c]			
Visit (V)	V1	V2 (Day 1)	V3—V7 [f, g, h] (every 2 wks)	V8	V9—V13 [f, g, h] (every 2 wks)	V14	V15—V19 [f, g, h] (every 2 wks)	V20	V21—26 [f, g, h] (every 2 wks)	V27 [g]	V28		V29	
Week	−4 to 0	0	2—10	12	14—22	24	26—34	36	38—48	50	52		62	
(Window)			(±3 days)										(±7 days)	
Weight	x										x			
Height	x													
Complete physical examination [o]	x											See Appendix 2		
Limited physical examination [p]		x		x		x		x			x		x	x
Single ECG	x [q]	x		x		x		x			x		x	x
Hematology [r]	x	x	Weeks 4 and 8 only	x		x		x			x		x	x
Chemistry [s]	x	x	Weeks 4 and 8 only	x		x		x			x		x	x
Hepatitis B & C testing	x [t]			x [u]				x [u]						
HIV testing	x [v]													
HbA_{1c}	x													

Appendix 1: Schedule of Activities

	Screen [a]	Treatment Period									Treat Compl/ Disc [b, c]	Add Treat Period [c]	EOS/ Safety Follow-Up [d]	EV [e]
Visit (V)	V1	V2 (Day 1)	V3—V7 [f, g, h] (every 2 wks)	V8	V9—V13 [f, g, h] (every 2 wks)	V14	V15—V19 [f, g, h] (every 2 wks)	V20	V21—26 [f, g, h] (every 2 wks)	V27 [g]	V28		V29	
Week	−4 to 0	0	2—10	12	14—22	24	26—34	36	38—48	50	52		62	
(Window)			(±3 days)										(±7 days)	
Fasting glucose [w]		x												
Fasting lipids [w, x]		x												
Pregnancy test (WOCBP only) [y]	x	x	x	x	x	x	x	x	x	x	x		x	
Urinalysis [z]	x													
Pre-bronchodilator spirometry [aa, bb]	x											See Appendix 2		
Post-bronchodilator spirometry [aa]	x	x		x		x		x			x			
Chest X-ray [cc]	x													
5STS	x	x		x		x		x			x			
Study drug administration [dd]		x	x	x	x	x	x	x	x	x				
Serum PK sample		x	Week 4 only	x		x		x			x		x	

Appendix 1: Schedule of Activities

	Screen [a]	Treatment Period										Add Treat Period [c]	EOS/ Safety Follow-Up [d]	EV [e]
											Treat Compl/ Disc [b, c]			
Visit (V)	V1	V2 (Day 1)	V3—V7 [f, g, h] (every 2 wks)	V8	V9—V13 [f, g, h] (every 2 wks)	V14	V15—V19 [f, g, h] (every 2 wks)	V20	V21—26 [f, g, h] (every 2 wks)	V27 [g]	V28		V29	
Week	−4 to 0	0	2—10	12	14—22	24	26—34	36	38—48	50	52		62	
(Window)			(±3 days)										(±7 days)	
Serum ADA sample		x	Week 4 only	x		x		x			x		x	
Plasma samples for biomarkers		x	Week 4 only	x		x		x			x		x	x
Serum samples for biomarkers		x	Week 4 only	x		x		x			x		x	x
Plasma citrate sample for biomarkers		x				x					x			
Blood sample for RNA analysis (PAXgene tube)		x									x	See Appendix 2		
Blood sample for specified DNA SNP analysis (mandatory)		x												
Blood sample for RBR (DNA WGS) (optional) [ee]		x												

Appendix 1: Schedule of Activities

	Screen [a]	Treatment Period									Treat Compl/ Disc [b, c]	Add Treat Period [c]	EOS/ Safety Follow-Up [d]	EV [e]
Visit (V)	V1	V2 (Day 1)	V3—V7 [f, g, h] (every 2 wks)	V8	V9—V13 [f, g, h] (every 2 wks)	V14	V15—V19 [f, g, h] (every 2 wks)	V20	V21—26 [f, g, h] (every 2 wks)	V27 [g]	V28		V29	
Week	−4 to 0	0	2—10	12	14—22	24	26—34	36	38—48	50	52		62	
(Window)			(±3 days)										(±7 days)	
Concomitant medications [ff]	x	x	x	x	x	x	x	x	x	x	x		x	x
Adverse events [gg]	x	x	x	x	x	x	x	x	x	x	x		x	x
Physical Activity Monitoring (For consenting patients at participating sites only) [hh]														
Physical activity measure		x		x		x					x	NA		
Physical activity monitor dispensation	x		Week 10		Week 22					x				
Intensive Pharmacokinetic Sampling (see Appendix 3) [ii]														

Appendix 1: Schedule of Activities

	Screen [a]	Treatment Period										Add Treat Period [c]	EOS/ Safety Follow-Up [d]	EV [e]
											Treat Compl/ Disc [b, c]			
Visit (V)	V1	V2 (Day 1)	V3—V7 [f, g, h] (every 2 wks)	V8	V9—V13 [f, g, h] (every 2 wks)	V14	V15—V19 [f, g, h] (every 2 wks)	V20	V21—26 [f, g, h] (every 2 wks)	V27 [g]	V28		V29	
Week	−4 to 0	0	2—10	12	14—22	24	26—34	36	38—48	50	52		62	
(Window)			(±3 days)										(±7 days)	
Airway Biomarker Substudy [ii]														
Pre-bronchodilator spirometry [aa, bb]		x									x	NA		
Serum samples for biomarkers	x													
Blood sample for RNA analysis (PAXgene tube)														x
Plethysmography [jj]		x									x			
HRCT [jj]		x									x [kk]			
Sputum (induced or produced spontaneously)	x	x [ll]	Week 4 only [ll]	x		x [ll]		x [ll]			x		x [ll]	x
Nasosorption		x	Week 4 only	x		x		x			x		x	x

5STS = five-repetition sit-to-stand test; ADA = anti-drug antibody; CAT = COPD Assessment Test; Compl = completion; COPD = chronic obstructive pulmonary disease; Disc = discontinuation; eCRF = electronic Case Report Form; eDiary = electronic diary; EOS = end of study; E-RS®:COPD = Evaluating Respiratory Symptoms in COPD; ; EV = exacerbation visit; EXACT® = EXAcerbations of Chronic Pulmonary Disease Tool; HbA_{1c} = hemoglobin A_{1c}; HRCT = high-resolution computed tomography; mMRC = Modified Medical Research Council (dyspnea scale); NA = not applicable; OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcome; RBR = Research Biosample Repository; Screen = screening; SGRQ-C = St. George's Respiratory Questionnaire-COPD; SNP = single nucleotide polymorphism; Treat = treatment; V = visit;; WGS = whole genome sequencing; wks = weeks; WOCBP = women of childbearing potential.

Notes: Visit windows for V3–V29 should be calculated in relation to the first dosing day (Day 1, V2 [Week 0]). On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion, as described in Section 4.5.1. A minimum screening period of 7 days prior to randomization is required.

[b] Patients who complete the study treatment period will return to the clinic for a treatment completion visit at Week 52. Patients who discontinue study drug prematurely should be asked to continue with all scheduled study assessments, with the exception of study drug administration and optional assessments (if applicable), through the end of the study. For these patients, telephone visits may replace certain in-clinic visits (see Footnote "h"). Patients who discontinue study drug prematurely and are unwilling to complete the study assessments should return to the clinic for a treatment discontinuation visit within 14 (+7) days of the event and will then enter the safety follow-up period, with end of study assessments 12 weeks after the final dose of study drug. Patients who are unwilling to complete the safety follow-up period should return to the clinic for treatment discontinuation visit as soon as possible and no later than 30 days after their final dose.

[c] Patients who enter the additional treatment period beyond Week 52 (see Section 3.1.1) will follow the schedule of assessments outlined in Appendix 2, beginning at Week 52.

[d] Patients who complete the study treatment period through the Week 52 treatment completion visit and do not enter the additional treatment period beyond Week 52 or OLE Study GB43374 will enter the safety follow-up period and undergo end of study assessments 12 weeks after the final dose of study drug.

[e] Patients enrolled in the Airway Biomarker Substudy who experience an acute COPD exacerbation will be asked to come to the clinic for an exacerbation visit prior to commencing treatment for the exacerbation, whenever possible. If not possible, patients treated on an outpatient basis should come to the clinic for an exacerbation visit within 1 week of the event and hospitalized patients should come to the clinic within 1 week of discharge. Note that the exacerbation visit applies only to patients enrolled in the Airway Biomarker Substudy; patients not enrolled in the substudy are not required to come to the clinic for an exacerbation visit.

[f] Unless otherwise specified, visits and assessments should occur every 2 weeks on even-numbered weeks (e.g., Week 4 [V4], Week 6 [V5], Week 8 [V6], etc.).

[g] For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, this visit (with the exception of Week 4 [V4] and Week 8 [V6]) may be performed by a trained nursing professional at the patient's home or another suitable location.

[h] For patients who discontinue study treatment prematurely, these visits (with the exception of Week 4 [V4] and Week 8 [V6]) may be performed via telephone to collect changes in health status and concomitant medications, if any. If the visit is conducted via telephone, vital signs do not need to be collected.

[i] Informed consent must be documented before any study-specific screening procedure is performed, and may not be obtained more than 28 days before initiation of study treatment (see Section 4.5.1).

[j] For patients who are current smokers (see Section 4.5.6).

[k] At specified visits, patients will be asked about their mask-wearing behavior.

[l] Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

[m] Patients are to complete the eDiary consisting of the EXACT-PRO and single item asking about rescue medication use at home once a day in the evening, prior to going to bed. At screening, patients will receive hands-on training in use of the eDiary, including review of the user guide. Patients will also be instructed to contact the site if they have any questions about the use of the device during screening or at any time during the study. Compliance with required use of the eDiary must be demonstrated as outlined in Section 4.5.13.1.

[n] Includes respiratory rate, pulse rate, peripheral oxygen saturation, and systolic and diastolic blood pressure, ideally while the patient is in a seated position after 5 minutes of rest, and temperature.

[o] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[p] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. New or worsened clinically significant abnormalities should be recorded on the Adverse Event eCRF.

[q] At screening, ECG recordings will be verified by an over-reader to confirm patient eligibility.

[r] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[s] Chemistry panel (serum or plasma) includes bicarbonate, sodium, potassium, chloride, glucose, urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, and AST.

[t] Includes HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a positive HCV antibody test at screening, an HCV RNA test with use of quantitative polymerase chain reaction must be performed. If a patient has a negative HBsAg and HBsAb and positive HBcAb at screening, an HBV DNA test must be performed.

[u] Only patients with an HBV DNA test value < 20 UI/mL at screening must undergo re-testing of HBV DNA at Week 12 and Week 36. If the HBV DNA test value at Week 12 or Week 36 is > 20 UI/mL, the Medical Monitor should be notified.

[v] HIV testing conducted where required by local regulations. HIV testing does not need to be repeated if performed within 3 months prior to screening.

[w] If patient has not fasted for 8 hours, patient must return to site for fasting blood draw within 2 weeks. All other scheduled activities at Visit 2 (including study drug administration) may be performed.

[x] Lipid panel includes total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

[y] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test result is positive, it must be reported immediately, and study drug will not be administered that day. The positive urine pregnancy result must be confirmed by a serum pregnancy test. Refer to Section 5.4.3 for reporting requirements for a patient with a positive pregnancy test.

[z] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[aa] Must be performed in the morning (i.e., prior to 1 p.m.).

[bb] COPD medications that may affect spirometry must be withheld until pre-bronchodilator spirometry measurements are completed (see Section 4.5.10.1 for details).

[cc] Chest X-ray must be performed unless results are available for chest X-ray or chest CT scan performed within 6 months of screening.

[dd] A minimum 8-day interval between study drug administrations is required (see Section 4.3.2.1 for details).

[ee] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. If the sample is not collected at the baseline visit, it may be collected at any later timepoint.

[ff] COPD medications, biologics, and immunomodulatory drugs used by the patients from 6 months prior to initiation of study drug through the end of the study should be recorded on the Concomitant Medications eCRF. All other medications used by the patient from 4 weeks prior to screening through the end of the study should be recorded on the Concomitant Medications eCRF.

[gg] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, including for all patients who discontinue study drug prematurely, all adverse events will be reported until 12 weeks after the final dose of study drug or until the last study visit, whichever is later. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study drug (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[hh] Performed only for patients *in the first phase of the study (first 1290 patients)* at participating sites who have provided written informed consent to participate (see Section 4.5.14). The physical activity monitor will be worn for a minimum of 1 week and up to 2 weeks during the monitoring period. Training and instructions on dispensing the device, information for patients, and data collection will be provided.

[ii] *Consent to participate in at least one of the optional exploratory assessments (intensive pharmacokinetic sampling and the Airway Biomarker Substudy) is required for patients who enroll in the second phase of the study (see Sections 4.5.15 and 4.5.16).*

[jj] May be performed up to 3 days prior to study visit.

[kk] HRCT *should not be performed* at the treatment discontinuation visit if patient discontinues prior to Week 12. For treatment discontinuations after Week12, HRCT should be performed.

[ll] *Sample should be taken at these timepoints only if feasible.*

Appendix 2
Schedule of Activities for Additional Treatment Period (beyond Week 52)

	Additional Treatment Period [a]							EOS/Safety Follow-Up [c]
							Treat Compl/Disc [b]	
Visit (V)	V28	V29—33 [d, e] (every 2 wks)	V34	V35—39 [d, e] (every 2 wks)	V40	V41—45 [d, e] (every 2 wks)	V46	V47
Week	52	54—62	64	66—74	76	78—86	88	98
(Window)	(±3 days)							(±7 days)
Smoking history	x		x		x		x	x
COPD exacerbation assessment	x [f]	x	x	x	x	x	x	x
SGRQ-C [g]	x							
mMRC [g]	x							
CAT [g]	x							
Daily eDiary	x							
Vital signs [h]	x	x	x	x	x	x	x	x
Weight	x							
Limited physical examination [i]	x		x		x		x	x
Single ECG	x		x		x		x	x
Hematology [j]	x		x		x		x	x
Chemistry [k]	x		x		x		x	x
Pregnancy test (WOCBP only) [l]	x	x	x	x	x	x	x	x
Post-bronchodilator spirometry [m]	x							
5STS	x							
Study drug administration [n]	x	x	x	x	x	x		

Appendix 2: Schedule of Activities for Additional Treatment Period (beyond Week 52)

	Additional Treatment Period [a]							
							Treat Compl/Disc [b]	EOS/Safety Follow-Up [c]
Visit (V)	V28	V29—33 [d, e] (every 2 wks)	V34	V35—39 [d, e] (every 2 wks)	V40	V41—45 [d, e] (every 2 wks)	V46	V47
Week	52	54—62	64	66—74	76	78—86	88	98
(Window)	(±3 days)							(±7 days)
Serum PK sample	x		x		x		x	x
Serum ADA sample	x		x		x		x	x
Plasma samples for biomarkers	x							
Serum samples for biomarkers	x							
Plasma citrate sample for biomarkers	x							
Blood sample for RNA analysis (PAXgene tube)	x							
Concomitant medications [o]	x	x	x	x	x	x	x	x
Adverse events [p]	x	x	x	x	x	x	x	x
Physical Activity Monitoring (For consenting patients at participating sites only) [q]								
Physical activity measure [q]	x							
Intensive Pharmacokinetic Sampling (see Appendix 3) [r]								

Appendix 2: Schedule of Activities for Additional Treatment Period (beyond Week 52)

	Additional Treatment Period [a]							
							Treat Compl/Disc [b]	EOS/Safety Follow-Up [c]
Visit (V)	V28	V29—33 [d, e] (every 2 wks)	V34	V35—39 [d, e] (every 2 wks)	V40	V41—45 [d, e] (every 2 wks)	V46	V47
Week	52	54—62	64	66—74	76	78—86	88	98
(Window)	(±3 days)							(±7 days)
Airway Biomarker Substudy [r]								
Pre-bronchodilator spirometry [m, s]	x							
Plethysmography [t]	x							
HRCT [t]	x							
Sputum (induced or produced spontaneously)	x							
Nasosorption	x							

5STS=five-repetition sit-to-stand test; ADA=anti-drug antibody; CAT=COPD Assessment Test; Compl=completion; COPD=chronic obstructive pulmonary disease; Disc=discontinuation; eCRF=electronic Case Report Form; eDiary=electronic diary; EOS=end of study; E-RS®:COPD=Evaluating Respiratory Symptoms in COPD; EXACT®=EXAcerbations of Chronic Pulmonary Disease Tool; HRCT=high-resolution computed tomography; mMRC=Modified Medical Research Council (dyspnea scale); OLE=open-label extension; PK=pharmacokinetic; PRO=patient-reported outcome; SGRQ-C=St. George's Respiratory Questionnaire-COPD; Treat=treatment; V=visit;; wks=weeks; WOCBP=women of childbearing potential.

Notes:

- Patients who are currently in the additional treatment period (Weeks 52–88) at the time the results of the interim analysis are available will move directly to the treatment completion visit 2 weeks after their last dose of study drug and will have the option of enrolling into OLE Study GB43374, if eligible, or will enter the safety follow-up period and undergo end of study assessments 12 weeks after the final dose of study drug.
- All visit windows should be calculated in relation to the first dosing day (Day 1, V2 [Week 0]).
- On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 2: Schedule of Activities for Additional Treatment Period (beyond Week 52)

[a] Patients who complete the Week 52 visit before the interim analysis will continue to receive blinded treatment beyond the 52-week treatment period for up to an additional 36 weeks or until the interim analysis results are known, whichever is sooner.

[b] Patients who complete the additional treatment period will return to the clinic for a treatment completion visit. Patients who discontinue study drug prematurely during the additional treatment period should return to the clinic for a treatment discontinuation visit within 14 (+7) days after the event and then enter the safety follow-up period and undergo end of study assessments 12 weeks after the final dose of study drug.

[c] Patients who complete the additional treatment period and do not enter OLE Study GB43374 will enter the safety follow-up period and undergo end of study assessments 12 weeks after the final dose of study drug.

[d] Unless otherwise specified, visits and assessments should occur every 2 weeks on even-numbered weeks (e.g., Week 54 [V29], Week 56 [V30], Week 58 [V31], etc.).

[e] For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, this visit may be performed by a trained nursing professional at the patient's home or another suitable location.

[f] At specified visits, patients will be asked about their mask-wearing behavior.

[g] Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

[h] Includes respiratory rate, pulse rate, peripheral oxygen saturation, and systolic and diastolic blood pressure, ideally while the patient is in a seated position after 5 minutes of rest, and temperature.

[i] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. New or worsened clinically significant abnormalities should be recorded on the Adverse Event eCRF.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[k] Chemistry panel (serum or plasma) includes bicarbonate, sodium, potassium, chloride, glucose, urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, and AST.

[l] Urine pregnancy tests will be performed at the specified visits. If a urine pregnancy test result is positive, it must be reported immediately, and study drug will not be administered that day. The positive urine pregnancy result must be confirmed by a serum pregnancy test. Refer to Section 5.4.3 for reporting requirements for a patient with a positive pregnancy test.

[m] Must be performed in the morning (i.e., prior to 1 p.m.).

[n] A minimum 8-day interval between study drug administrations is required (see Section 4.3.2.1 for details).

[o] All concomitant medications used through the end of the study should be recorded on the Concomitant Medications eCRF.

[p] All adverse events will be reported until 12 weeks after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study drug (see Section 5.6).The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[q] Performed only for patients *in the first phase of the study (first 1290 patients)* at participating sites who have provided written informed consent to participate (see Section 4.5.14).

[r] *Consent to participate in at least one of the optional exploratory assessments (intensive pharmacokinetic sampling and the Airway Biomarker Substudy) is required for patients who enroll in the second phase of the study (see Sections 4.5.15 and 4.5.16).*

[s] COPD medications that may affect spirometry must be withheld until pre-bronchodilator spirometry measurements are completed (see Section 4.5.10.1).

[t] May be performed up to 3 days prior to study visit.

Appendix 3
Schedule of Intensive Pharmacokinetic Sampling and Assessments (Consenting Patients at Participating Sites Only)

Visit [a]	Timepoint [b]	Sample Type
2-a [c]	3 days after Visit 2 (±1 day)	Serum PK sample
2-b [c]	7 days after Visit 2 (±1 day)	Serum PK sample
2-c [c]	10 days after Visit 2 (±1 day)	Serum PK sample
26 [c]	Visit 26 (see Appendix 1)	Serum PK sample
26-a	7 days after Visit 26 (±1 day)	Serum PK sample Single ECG [d]
28-a [c, e]	28 days after Visit 28 (±14 days)	Serum PK sample

OLE = open-label extension; PK = pharmacokinetic.

Notes: Additional PK samples will be collected from approximately 240 consenting patients; patients with incomplete intensive PK sampling sets may be replaced. Performed only for patients at participating sites who have provided written informed consent to participate (see Section 4.5.15). PK samples are to be collected prior to dosing, when applicable, and at approximately the same time each day.

a PK sampling visits that are between regular study visits are given a letter suffix. These timepoint designations are not reflected in the schedule of activities in Appendix 1.

b Visit windows should be calculated in relation to the first dosing day (Day 1, Visit 2 [Week 0]).

c For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, this visit may be performed by a trained nursing professional at the patient's home or another suitable location.

d Single ECG should be performed within 1 hour prior to serum PK sample collection.

e For patients entering the additional treatment period or enrolling in OLE Study GB43374, Visit 28a should not be conducted.

Appendix 4
St. George's Respiratory Questionnaire

<u>Do not reproduce or distribute</u>. The Sponsor will provide sites with all instruments to be completed in this study.

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life.

We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

ID :_____

Date :_____/_____/_____(dd/mm/yy)

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

Version: 1st Sept 2005

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P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Cranmer Terrace
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

St. George's Respiratory Questionnaire

PART 1

Questions about how much respiratory trouble you have.

Please check (✓) **ONE** box for each question:

Question 1. I cough:

most days a week ..... ☐ a

several days a week……. ☐ b

only with respiratory infections… ☐ c

not at all……...… ☐ d

Question 2. I bring up phlegm (sputum):

most days a week ..... ☐ a

several days a week……..... ☐ b

only with respiratory infections… ☐ c

not at all…… ☐ d

Question 3. I have shortness of breath:

most days a week ..... ☐ a

several days a week……... ☐ b

not at all……. ☐ c

Question 4. I have attacks of wheezing:

most days a week ..... ☐ a

several days a week……..... ☐ b

a few days a month..... ☐ c

only with respiratory infections… ☐ d

not at all……..… ☐ e

St. George's Respiratory Questionnaire
PART 1

Question 5. How many respiratory attacks did you have during the last year?

3 or more attacks…..... ☐ a

1 or 2 attacks…….……... ☐ b

none…….…..... ☐ c

Question 6. How often do you have good days (with few respiratory problems)?

no good days…..…..... ☐ a

a few good days…...…...…….…..... ☐ b

most days are good…..…..... ☐ c

every day is good…..…… ☐ d

Question 7. If you wheeze, is it worse when you get up in the morning?

No……..…… ☐

Yes…… ☐

St. George's Respiratory Questionnaire
PART 2

8. ***How would you describe your respiratory problems?***

Please check (✓) ***ONE***:

Cause me a lot of problems or are the most important physical problem I have…… ☐ a

Cause me a few problems……..…….☐ b

Cause no problems……..……..☐ c

9. ***Questions about what activities usually make you feel breathless.***

For each statement please check (✓) in ***the box*** that applies to you **these days**:

	True	**False**	
Washing or dressing yourself……..…….……..	☐	☐	a
Walking around the house…….…….……	☐	☐	b
Walking outside on level ground…….……..	☐	☐	c
Walking up a flight of stairs…….....	☐	☐	d
Walking up hills…….……..…….....	☐	☐	e

St. George's Respiratory Questionnaire
PART 2

10. ***Some more questions about your cough and breathlessness.***

For each statement please check (✓) in ***the box*** that applies to you **these days**:

	True	False	
Coughing hurts……....	☐	☐	a
Coughing makes me tired……..……	☐	☐	b
I am short of breath when I talk…….....	☐	☐	c
I am short of breath when I bend over……..	☐	☐	d
My coughing or breathing disturbs my sleep…….....	☐	☐	e
I get exhausted easily……...……	☐	☐	f

11. ***Questions about other effects that your respiratory problems may have on you.***

For each statement please check (✓) in ***the box*** that applies to you **these days:**

	True	False	
My cough or breathing is embarrassing in public ……..	☐	☐	a
My respiratory problems are a nuisance to my family, friends or neighbors……	☐	☐	b
I get afraid or panic when I cannot catch my breath……..	☐	☐	c
I feel that I am not in control of my respiratory problems……	☐	☐	d
I have become frail or an invalid because of my respiratory problems….	☐	☐	e
Exercise is not safe for me…….	☐	☐	f
Everything seems too much of an effort……..	☐	☐	g

St. George's Respiratory Questionnaire
PART 2

12. ***These are questions about how your activities might be affected by your respiratory problems.***

For each statement please check (✓) in ***the box*** that applies to you **because of your respiratory problems**:

	True	False	
I take a long time to get washed or dressed……	☐	☐	a
I cannot take a bath or shower, or I take a long time to do it……	☐	☐	b
I walk slower than other people my age, or I stop to rest……	☐	☐	c
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐	d
If I walk up one flight of stairs, I have to go slowly or stop….....	☐	☐	e
If I hurry or walk fast, I have to stop or slow down……..	☐	☐	f
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf …… .....….	☐	☐	g
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim……..……..	☐	☐	h

13. We would like to know how your respiratory problems <u>usually</u> affect your daily life.

For each statement please check (✓) in ***the box*** that applies to you ***because of your respiratory problems***:

	True	False	
I cannot play sports or do other physical activities……	☐	☐	a
I cannot go out for entertainment or recreation……	☐	☐	b
I cannot go out of the house to do the shopping……..……..	☐	☐	c
I cannot do household chores……	☐	☐	d
I cannot move far from my bed or chair…….	☐	☐	e

St. George's Respiratory Questionnaire
PART 2

14. How do your respiratory problems affect you?

Please check (✓) ***ONE***:

They do not stop me from doing anything I would like to do…….. ☐ a

They stop me from doing one or two things I would like to do…… ☐ b

They stop me from doing most of the things I would like to do……... ☐ c

They stop me from doing everything I would like to do……..... ☐ d

Thank you for completing this questionnaire.

Before you finish, would you please make sure that you have answered all the questions.

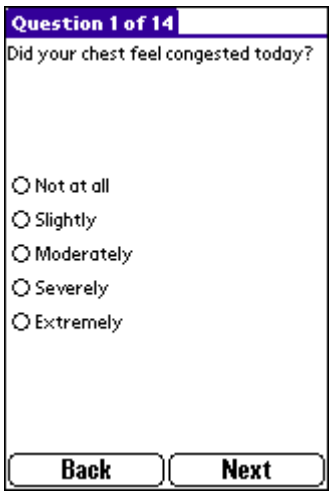
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Daily eDiary

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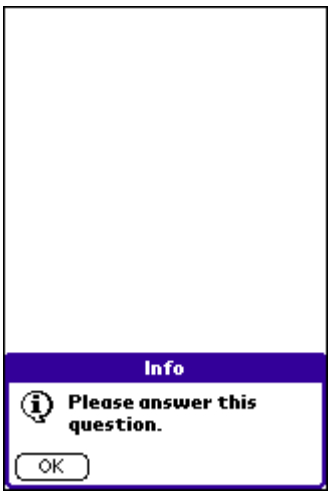
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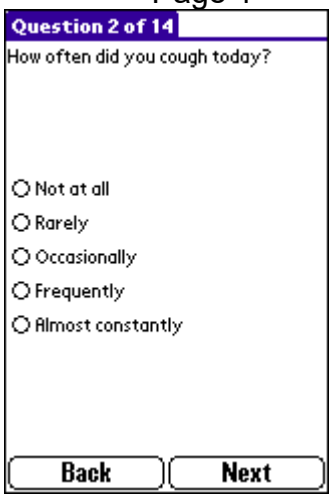


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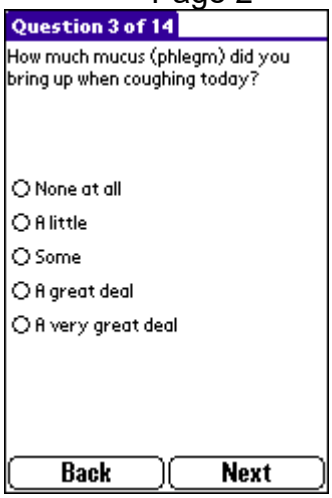


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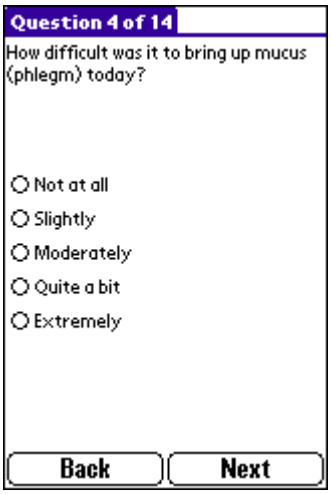




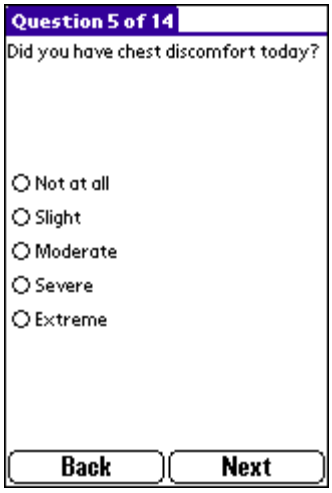
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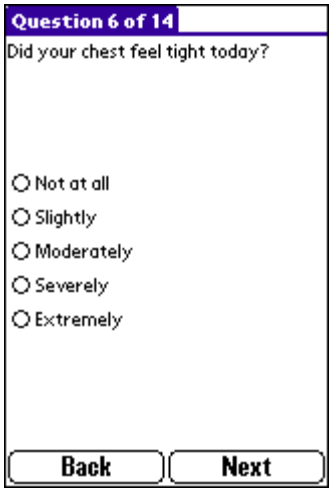
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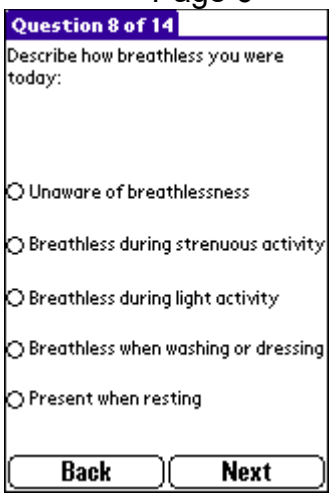
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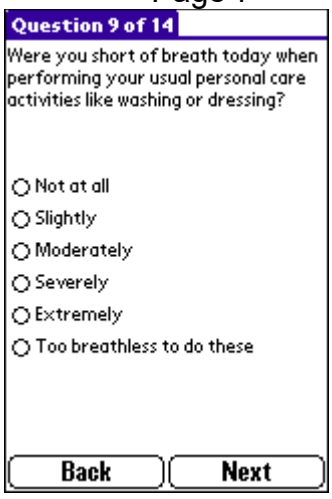
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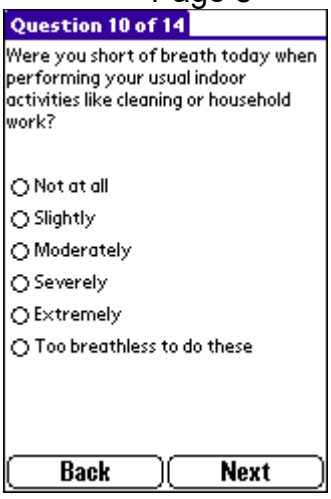
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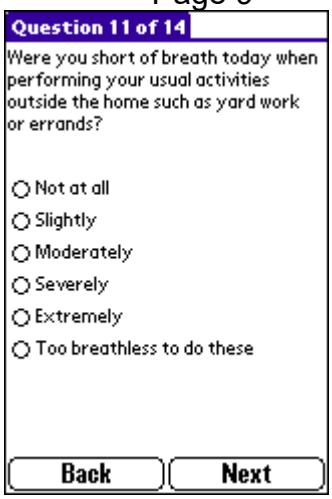
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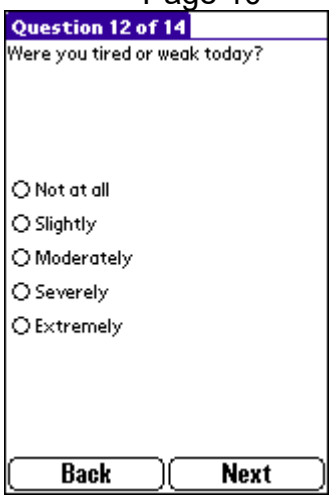
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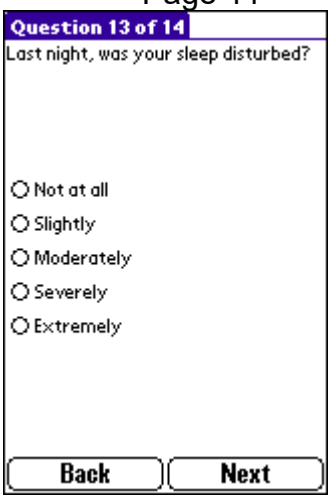
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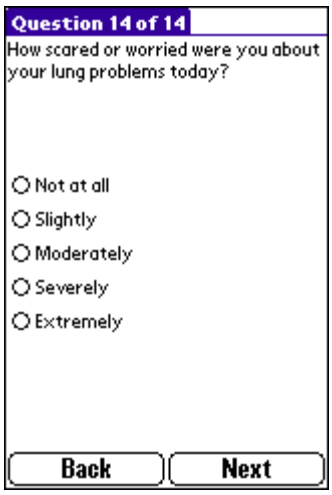
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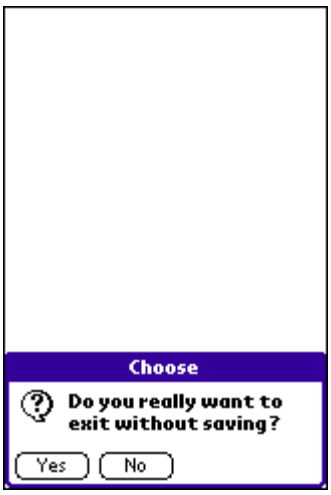
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Rescue Therapy Use

Did you take any rescue medication for your COPD symptoms (e.g. dyspnea, sputum volume, and sputum purulence)?

- No, I did not take any rescue medication
- Yes, I used a rescue inhaler
- Yes, I used a nebulizer (breathing machine)

Appendix 6
Modified Medical Research Council Dyspnea Scale

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Modified Medical Research Council Dyspnea Scale

Please select the statement that best describes you with respect to your COPD.

__"I only get breathless with strenuous exercise."

__"I get short of breath when hurrying on the level or up a slight hill."

__"I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level."

__"I stop for breath after walking 100 yards or after a few minutes on the level."

__"I am too breathless to leave the house."

Appendix 7
COPD Assessment Test™

<u>Do not reproduce or distribute</u>. The Sponsor will provide sites with all instruments to be completed in this study.



Your name:_____

Today's date:_____

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy [0] [X] [2] [3] [4] [5] I am very sad

			SCORE
I never cough	[0] [1] [2] [3] [4] [5]	I cough all the time	☐
I have no phlegm (mucus) in my chest at all	[0] [1] [2] [3] [4] [5]	My chest is completely full of phlegm (mucus)	☐
My chest does not feel tight at all	[0] [1] [2] [3] [4] [5]	My chest feels very tight	☐
When I walk up a hill or one flight of stairs I am not breathless	[0] [1] [2] [3] [4] [5]	When I walk up a hill or one flight of stairs I am very breathless	☐
I am not limited doing any activities at home	[0] [1] [2] [3] [4] [5]	I am very limited doing activities at home	☐
I am confident leaving my home despite my lung condition	[0] [1] [2] [3] [4] [5]	I am not at all confident leaving my home because of my lung condition	☐
I sleep soundly	[0] [1] [2] [3] [4] [5]	I don't sleep soundly because of my lung condition	☐
I have lots of energy	[0] [1] [2] [3] [4] [5]	I have no energy at all	☐

TOTAL SCORE ☐☐

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Appendix 8
Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

The investigator will use the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (HHS 2017), with slight modifications for clarity and for alignment with internal practices, for assessing the severity of each adverse event reported during the study.

Table 1 Severity Grading for Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cardiovascular				
Arrhythmia (by ECG or physical examination) (Specify type if applicable)	No symptoms and no intervention indicated	No symptoms and non-urgent intervention indicated	Non–life-threatening symptoms and non-urgent intervention indicated	Life-threatening arrhythmia or urgent intervention indicated
Hypertension (with the lowest reading taken after repeat testing during a visit): ≥18 years of age	140 to <160 mmHg systolic or 90 to <100 mmHg diastolic [a]	≥160 to <180 mmHg systolic or ≥100 to <110 mmHg diastolic [a]	≥180 mmHg systolic or ≥110 mmHg diastolic [a]	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) or hospitalization indicated
Hypertension (with the lowest reading taken after repeat testing during a visit): <18 years of age [b]	>120 mmHg systolic or >80 mmHg diastolic, but systolic and diastolic <95th percentile adjusted for age, height, and sex	≥95th to <5 mmHg above the 99th adjusted for age, height, and sex (systolic and/or diastolic) [a]	≥5 mmHg above the 99th percentile adjusted for age, height, and sex [a] (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) or hospitalization indicated

[a] When systolic and diastolic blood pressures meet criteria for different grades, the higher grade should be used.

[b] Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128(Suppl 5):S213–56.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cardiovascular (cont.)				
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms and IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac ischemia or infarction (Report the most appropriate term)	—	—	New symptoms with ischemia (stable angina) or new testing consistent with ischemia	Unstable angina or acute myocardial infarction
Heart failure	No symptoms and laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) or intervention indicated (e.g., oxygen)	Life-threatening consequences or urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	—	Symptoms and no transfusion indicated	Symptoms and transfusion of $\leq$2 units packed RBCs (for children, packed RBCs $\leq$10 cc/kg) indicated	Life-threatening hypotension or transfusion of $>$2 units packed RBCs (for children, packed RBCs $>$10 cc/kg) indicated
Prolonged PR interval or AV block: $>$16 years of age (Report the most appropriate term)	PR interval 0.21 to $<$0.25 seconds	PR interval $\geq$0.25 seconds or Type I second-degree AV block	Type II second-degree AV block or ventricular pause $\geq$3.0 seconds	Complete AV block
Prolonged PR interval or AV block: $\leq$16 years of age (Report the most appropriate term)	First-degree AV block (PR interval $>$ normal for age and rate)	Type I second-degree AV block	Type II second-degree AV block or ventricular pause $\geq$3.0 seconds	Complete AV block

AV = atrioventricular.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cardiovascular (cont.)				
Prolonged QTc interval (corrected per Bazett's formula)	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds or ≥0.06 seconds above baseline	Life-threatening consequences (e.g., torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or embolism (Report the most appropriate term)	—	Symptoms and no intervention indicated	Symptoms and intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
Dermatologic				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	—	—
Bruising	Localized to one area	Localized to more than one area	Generalized	—
Cellulitis	—	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	—	—

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Dermatologic (cont.)				
Hypopigmentation	Slight or localized causing no or minimal interference with usual social and functional activities	Marked or generalized causing greater than minimal interference with usual social and functional activities	—	—
Petechiae	Localized to one area	Localized to more than one area	Generalized	—
Pruritus [c] (without skin lesions)	Itching causing no or minimal interference with usual social and functional activities	Itching causing greater than minimal interference with usual social and functional activities	Itching causing inability to perform usual social and functional activities	—
Rash (Specify type, if applicable)	Localized rash	Diffuse rash or target lesions	Diffuse rash and vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions or ulceration of mucous membrane involving two or more distinct mucosal sites or Stevens-Johnson syndrome or toxic epidermal necrolysis
Endocrine and Metabolic				
Diabetes mellitus	Controlled without medication	Controlled with medication or modification of current medication regimen	Uncontrolled despite treatment modification or hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)

[c] For pruritus associated with injections or infusions, see "Site Reactions to Injections and Infusions"

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Endocrine and Metabolic (cont.)				
Gynecomastia	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing pain with greater than minimal interference with usual social and functional activities	Disfiguring changes and symptoms requiring intervention or causing inability to perform usual social and functional activities	—
Hyperthyroidism	No symptoms and abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities or thyroid suppression therapy indicated	Symptoms causing inability to perform usual social and functional activities or uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms and abnormal laboratory value	Symptoms causing greater than minimal interference with usual social and functional activities or thyroid replacement therapy indicated	Symptoms causing inability to perform usual social and functional activities or uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (disorder characterized by fat loss in the face, extremities, and buttocks)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	Disfiguring changes	—

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Endocrine and Metabolic (cont.)				
Lipohypertrophy (disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen)	Detectable by study participant, caregiver, or physician and causing no or minimal interference with usual social and functional activities	Obvious on visual inspection and causing greater than minimal interference with usual social and functional activities	Disfiguring changes	—
Gastrointestinal				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences or aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms and intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or distension (Report the most appropriate term)	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	—
Cholecystitis	—	Symptoms and medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Gastrointestinal (cont.)				
Constipation	—	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea: ≥1 year of age	Transient or intermittent episodes of unformed stools or increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools or Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools over baseline per 24-hour period or IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Diarrhea: <1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools or mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or odynophagia (Report the most appropriate term and specify location)	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or stomatitis (Report the most appropriate term and specify location)	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations or mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) or tissue necrosis or diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent nausea and no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for >48 hours or rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Gastrointestinal (cont.)				
Pancreatitis	—	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	—	—	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social and functional activities or medical intervention indicated	Symptoms causing inability to perform usual social and functional activities or operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal discharge	Visible discharge	Discharge requiring the use of pads	—	—
Vomiting	Transient or intermittent vomiting and no or minimal interference with oral intake	Frequent vomiting episodes and no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Musculoskeletal				
Arthralgia	Joint pain causing no or minimal interference with usual social and functional activities	Joint pain causing greater than minimal interference with usual social and functional activities	Joint pain causing inability to perform usual social and functional activities	Disabling joint pain causing inability to perform basic self-care functions

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Musculoskeletal (cont.)				
Arthritis	Joint stiffness or swelling causing no or minimal interference with usual social and functional activities	Joint stiffness or swelling causing greater than minimal interference with usual social and functional activities	Joint stiffness or swelling causing inability to perform usual social and functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social and functional activities	Muscle pain causing greater than minimal interference with usual social and functional activities	Muscle pain causing inability to perform usual social and functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	—	No symptoms but with radiographic findings and no operative intervention indicated	Bone pain with radiographic findings or operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia: ≥30 years of age	BMD t-score −2.5 to −1	—	—	—
Osteopenia: <30 years of age	BMD z-score −2 to −1	—	—	—
Osteoporosis: ≥30 years of age	—	BMD t-score < −2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Osteoporosis: <30 years of age	—	BMD z-score < −2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

BMD = bone mineral density.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic				
Acute CNS ischemia	—	—	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered mental status (for dementia, see cognitive, behavioral, or attentional disturbance below)	Changes causing no or minimal interference with usual social and functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social and functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social and functional activities	Delirium or obtundation or coma
Ataxia	Symptoms causing no or minimal interference with usual social and functional activities or no symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, behavioral, or attentional disturbance (includes dementia and attention deficit disorder) (Specify type, if applicable)	Disability causing no or minimal interference with usual social and functional activities or specialized resources not indicated	Disability causing greater than minimal interference with usual social and functional activities or specialized resources on part-time basis indicated	Disability causing inability to perform usual social and functional activities or specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions or institutionalization indicated

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic (cont.)				
Developmental delay < 18 years of age (Specify type, if applicable)	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions or hospitalization indicated or headache with significant impairment of alertness or other neurologic function
Neuromuscular weakness (includes myopathy and neuropathy) (Specify type, if applicable)	Minimal muscle weakness causing no or minimal interference with usual social and functional activities or no symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social and functional activities	Muscle weakness causing inability to perform usual social and functional activities	Disabling muscle weakness causing inability to perform basic self-care functions or respiratory muscle weakness impairing ventilation

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Neurologic (cont.)				
Neurosensory alteration (includes paresthesia and painful neuropathy) (Specify type, if applicable)	Minimal paresthesia causing no or minimal interference with usual social and functional activities or no symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure, new onset: ≥ 18 years of age	—	—	1–3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Seizure, new onset: < 18 years of age (includes new or preexisting febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes or ≥ 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Seizure, preexisting (excludes preexisting febrile seizures)	—	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) or difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness and hospitalization or intervention required	—
Pregnancy, Puerperium, and Perinatal				
Stillbirth	—	—	Fetal death occurring at ≥ 20 weeks gestational age	—

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Pregnancy, Puerperium, and Perinatal (cont.)				
Preterm birth	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous abortion (a pregnancy loss occurring at < 20 weeks gestational age, also known as miscarriage)	Chemical pregnancy	Uncomplicated spontaneous abortion	Complicated spontaneous abortion	—
Psychiatric				
Insomnia	Mild difficulty falling asleep or staying asleep or mild difficulty caused by early morning awakening, causing no or minimal interference with usual social and functional activities	Moderate difficulty falling asleep or staying asleep, or moderate difficulty caused by early morning awakening, causing greater than minimal interference with usual social and functional activities	Severe difficulty falling asleep or staying asleep or severe difficulty caused by early morning awakening, causing inability to perform usual social and functional activities and requiring intervention or hospitalization	—
Psychiatric disorder (includes anxiety, depression, mania, and psychosis) (Specify disorder)	Symptoms with intervention not indicated or behavior causing no or minimal interference with usual social and functional activities	Symptoms with intervention indicated or behavior causing greater than minimal interference with usual social and functional activities	Symptoms with hospitalization indicated or behavior causing inability to perform usual social and functional activities	Threatens harm to self or others or acute psychosis or behavior causing inability to perform basic self-care functions

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Psychiatric (cont.)				
Suicidal ideation or suicide attempt (Report the most appropriate term)	Preoccupied with thoughts of death and no wish to kill oneself	Preoccupied with thoughts of death and wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so or hospitalization indicated	Suicide attempted
Respiratory				
Acute bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70 to <80% of predicted or mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50% to <70% of predicted or symptoms with intervention indicated or symptoms causing greater than minimal interference with usual social and functional activities	Forced expiratory volume in 1 second or peak flow 25% to <50% of predicted or symptoms causing inability to perform usual social and functional activities	Forced expiratory volume in 1 second or peak flow <25% of predicted or life-threatening respiratory or hemodynamic compromise or intubation
Dyspnea or respiratory distress (Report the most appropriate term)	Dyspnea on exertion with no or minimal interference with usual social and functional activities or wheezing or minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social and functional activities or nasal flaring or intercostal retractions or pulse oximetry 90% to <95%	Dyspnea at rest causing inability to perform usual social and functional activities or pulse oximetry <90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Sensory				
Hearing loss (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram): ≥12 years of age	—	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) or non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
Hearing loss (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram): <12 years of age	>20 dB hearing loss at ≤4 kHz	>20 dB hearing loss at >4 kHz	>20 dB hearing loss at ≥3 kHz in one ear with additional speech language related services indicated (where available) or hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language–related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social and functional activities and intervention not indicated	Symptoms causing greater than minimal interference with usual social and functional activities or intervention indicated	Symptoms causing inability to perform usual social and functional activities	—
Uveitis	No symptoms and detectable uveitis on examination	Anterior uveitis with symptoms or medical intervention indicated	Posterior uveitis or panuveitis or operative intervention indicated	Uveitis with disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social and functional activities	Vertigo causing greater than minimal interference with usual social and functional activities	Vertigo causing inability to perform usual social and functional activities	Disabling vertigo causing inability to perform basic self-care functions

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Sensory (cont.)				
Visual changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social and functional activities	Visual changes causing greater than minimal interference with usual social and functional activities	Visual changes causing inability to perform usual social and functional activities	Visual changes with disabling visual loss in affected eye(s)
Systemic				
Acute allergic reaction	Localized urticaria (wheals) with no intervention indicated	Localized urticaria with intervention indicated or mild angioedema with no intervention indicated	Generalized urticaria or angioedema with intervention indicated or symptoms of mild bronchospasm	Acute anaphylaxis or life-threatening bronchospasm or laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	—
Cytokine-release syndrome (disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath)	Mild signs and symptoms and therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated and responds promptly to symptomatic treatment or prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms or recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Systemic (cont.)				
Fatigue or malaise (Report the most appropriate term)	Symptoms of fatigue or malaise causing no or minimal interference with usual social and functional activities	Symptoms of fatigue or malaise causing greater than minimal interference with usual social and functional activities	Symptoms of fatigue or malaise causing inability to perform usual social and functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to $<$38.6°C or 100.4 to $<$101.5°F	$\geq$38.6 to $<$39.3°C or $\geq$101.5 to $<$102.7°F	$\geq$39.3 to $<$40.0°C or $\geq$102.7 to $<$104.0°F	$\geq$40.0°C or $\geq$104.0°F
Pain (not associated with study agent injections and not specified elsewhere) (Specify location)	Pain causing no or minimal interference with usual social and functional activities	Pain causing greater than minimal interference with usual social and functional activities	Pain causing inability to perform usual social and functional activities	Disabling pain causing inability to perform basic self-care functions or hospitalization indicated
Serum sickness (disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea)	Mild signs and symptoms	Moderate signs and symptoms and intervention indicated (e.g., antihistamines)	Severe signs and symptoms and higher level intervention indicated (e.g., corticosteroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Systemic (cont.)				
Underweight: > 5 to 19 years of age	WHO BMI z-score [d] < –1 to –2	WHO BMI z-score [d] < –2 to –3	WHO BMI z-score [d] < –3	WHO BMI z-score [d] < –3 with life-threatening consequences
Underweight: 2 to 5 years of age	WHO weight-for-height z-score [e] < –1 to –2	WHO weight-for-height z-score [e] < –2 to –3	WHO weight-for-height z-score [e] < –3	WHO weight-for-height z-score [e] < –3 with life-threatening consequences
Underweight: < 2 years of age	WHO weight-for-length z-score [e] < –1 to –2	WHO weight-for-length z-score [e] < –2 to –3	WHO weight-for-length z-score [e] < –3	WHO weight-for-length z-score [e] < –3 with life-threatening consequences
Unintentional weight loss (excludes postpartum weight loss)	—	5% to < 9% loss in body weight from baseline	≥ 9% to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline or aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Urinary				
Urinary tract obstruction	—	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

BMI = body mass index; WHO = World Health Organization.

[d] WHO reference tables for participants > 5 to 19 years of age: http://www.who.int/growthref/who2007_bmi_for_age/en/.

[e] WHO reference tables for participants ≤ 5 years of age: http://www.who.int/childgrowth/standards/chart_catalogue/en/.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Site Reactions to Injections and Infusions [f]				
Injection-site pain or tenderness [f]	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social and functional activities	Pain or tenderness causing inability to perform basic self-care function or hospitalization indicated
Injection-site erythema, redness, induration, or swelling: [f] >15 years of age (Report the most appropriate term; report multiple events if appropriate)	2.5 to <5 cm in diameter or 6.25 to <25 cm^2 surface area [g] and symptoms causing no or minimal interference with usual social and functional activities	≥5 to <10 cm in diameter or ≥25 to <100 cm^2 surface area [g] or symptoms causing greater than minimal interference with usual social and functional activities	≥10 cm in diameter or ≥100 cm^2 surface area [g] or ulceration or secondary infection or phlebitis or sterile abscess or drainage or symptoms causing inability to perform usual social and functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection-site erythema, redness, induration, or swelling: [f] ≤15 years of age (Report the most appropriate term; report multiple events if appropriate)	≤2.5 cm in diameter [g]	>2.5 cm in diameter with <50% surface area [g] of the extremity segment involved (e.g., upper arm or thigh)	≥50% surface area [g] of the extremity segment involved (e.g., upper arm or thigh) or ulceration or secondary infection or phlebitis or sterile abscess or drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

[f] Refer to Section 5.3.5.3 for instructions on reporting injection-site reactions to study treatment (if applicable). For reactions to drugs other than study treatment, report the most appropriate term and report multiple events, if applicable.

[g] Grading should be based on the greatest single diameter or measured surface area.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Site Reactions to Injections and Infusions (cont.) [f]				
Injection-site pruritus [f]	Itching localized to the injection site that is relieved spontaneously or requires treatment for < 48 hours	Itching beyond the injection site that is not generalized or itching localized to the injection site that requires treatment for ≥ 48 hours	Generalized itching causing inability to perform usual social and functional activities	—
Chemistries				
Acidosis	—	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, low	3.0 g/dL to < LLN (30 g/L to < LLN)	≥ 2.0 to < 3.0 g/dL (≥ 20 to < 30 g/L)	< 2.0 g/dL (< 20 g/L)	—
Alkaline phosphatase, high	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Alkalosis	—	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, high (Report the most appropriate term)	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Amylase (pancreatic) or amylase (total), high (Report the most appropriate term)	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN

LLN = lower limit of normal; ULN = upper limit of normal.

[f] Refer to Section 5.3.5.3 for instructions on reporting injection-site reactions to study treatment (if applicable). For reactions to drugs other than study treatment, report the most appropriate term and report multiple events, if applicable.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
AST or SGOT, high (Report the most appropriate term)	1.25 to < 2.5 × ULN	2.5 to < 5.0 × ULN	5.0 to < 10.0 × ULN	≥ 10.0 × ULN
Bicarbonate, low	16.0 mEq/L to < LLN (16.0 mmol/L to < LLN)	11.0 to < 16.0 mEq/L (11.0 to < 16.0 mmol/L)	8.0 to < 11.0 mEq/L (8.0 to < 11.0 mmol/L)	< 8.0 mEq/L (< 8.0 mmol/L)
Bilirubin (direct), high: > 28 days of age	—	—	> ULN with other signs and symptoms of hepatotoxicity	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
Bilirubin (direct), high: ≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL [h]	> 2 mg/dL [h]
Bilirubin (total), high: > 28 days of age	1.1 to < 1.6 × ULN	1.6 to < 2.6 × ULN	2.6 to < 5.0 × ULN	≥ 5.0 × ULN
Bilirubin (total), high: ≤ 28 days of age	See Table 2			
Calcium, high: ≥ 7 days of age	10.6 to < 11.5 mg/dL (2.65 to < 2.88 mmol/L)	11.5 to < 12.5 mg/dL (2.88 to < 3.13 mmol/L)	12.5 to < 13.5 mg/dL (3.13 to < 3.38 mmol/L)	≥ 13.5 mg/dL (≥ 3.38 mmol/L)
Calcium, high: < 7 days of age	11.5 to < 12.4 mg/dL (2.88 to < 3.10 mmol/L)	12.4 to < 12.9 mg/dL (3.10 to < 3.23 mmol/L)	12.9 to < 13.5 mg/dL (3.23 to < 3.38 mmol/L)	≥ 13.5 mg/dL (≥ 3.38 mmol/L)
Calcium (ionized), high	> ULN to < 6.0 mg/dL (> ULN to < 1.5 mmol/L)	6.0 to < 6.4 mg/dL (1.5 to < 1.6 mmol/L)	6.4 to < 7.2 mg/dL (1.6 to < 1.8 mmol/L)	≥ 7.2 mg/dL (≥ 1.8 mmol/L)

LLN = lower limit of normal; ULN = upper limit of normal.

[h] Direct bilirubin > 1.5 mg/dL in a participant ≤ 28 days of age should be graded as Grade 2, if < 10% of the total bilirubin.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Calcium, low: ≥7 days of age	7.8 to <8.4 mg/dL (1.95 to <2.10 mmol/L)	7.0 to <7.8 mg/dL (1.75 to <1.95 mmol/L)	6.1 to <7.0 mg/dL (1.53 to <1.75 mmol/L)	<6.1 mg/dL (<1.53 mmol/L)
Calcium, low: <7 days of age	6.5 to <7.5 mg/dL (1.63 to <1.88 mmol/L)	6.0 to <6.5 mg/dL (1.50 to <1.63 mmol/L)	5.50 to <6.0 mg/dL (1.38 to <1.50 mmol/L)	<5.50 mg/dL (<1.38 mmol/L)
Calcium (ionized), low	<LLN to 4.0 mg/dL (<LLN to 1.0 mmol/L)	3.6 to <4.0 mg/dL (0.9 to <1.0 mmol/L)	3.2 to <3.6 mg/dL (0.8 to <0.9 mmol/L)	<3.2 mg/dL (<0.8 mmol/L)
Cardiac troponin I, high	—	—	—	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine kinase, high	3 to <6 × ULN	6 to <10 × ULN	10 to <20 × ULN	≥20 × ULN
Creatinine, high	1.1 to 1.3 × ULN	>1.3 to 1.8 × ULN or increase to 1.3 to <1.5 × baseline [i]	>1.8 to <3.5 × ULN or increase to 1.5 to <2.0 × baseline [i]	≥3.5 × ULN or increase to ≥2.0 × baseline [i]
Creatinine clearance or eGFR, low (Report the most appropriate term)	—	<90 to 60 mL/min or mL/min/1.73 m^2 or 10% to <30% decrease from baseline [j]	<60 to 30 mL/min or mL/min/1.73 m^2 or 30% to <50% decrease from baseline [j]	<30 mL/min or mL/min/1.73 m^2 or ≥50% decrease from baseline [j] or dialysis needed

eGFR = estimated glomerular filtration rate; LLN = lower limit of normal; ULN = upper limit of normal.

[i] For participant with normal baseline value, grade should be based on current value relative to ULN. For participant with elevated baseline value, grade should be based on current value relative to baseline value.

[j] For participant with normal baseline value, grade should be based on current value. For participant with elevated baseline value, grade should be based on current value relative to baseline value.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Glucose (fasting), high	110 to 125 mg/dL (6.11 to < 6.95 mmol/L)	> 125 to 250 mg/dL (6.95 to < 13.89 mmol/L)	> 250 to 500 mg/dL (13.89 to < 27.75 mmol/L)	≥ 500 mg/dL (≥ 27.75 mmol/L)
Glucose (non-fasting), high	116 to 160 mg/dL (6.44 to < 8.89 mmol/L)	> 160 to 250 mg/dL (8.89 to < 13.89 mmol/L)	> 250 to 500 mg/dL (13.89 to < 27.75 mmol/L)	≥ 500 mg/dL (≥ 27.75 mmol/L)
Glucose, low: ≥ 28 days of age	55 to 64 mg/dL (3.05 to < 3.55 mmol/L)	40 to < 55 mg/dL (2.22 to < 3.05 mmol/L)	30 to < 40 mg/dL (1.67 to < 2.22 mmol/L)	< 30 mg/dL (< 1.67 mmol/L)
Glucose, low: < 28 days of age	50 to 54 mg/dL (2.78 to < 3.00 mmol/L)	40 to < 50 mg/dL (2.22 to < 2.78 mmol/L)	30 to < 40 mg/dL (1.67 to < 2.22 mmol/L)	< 30 mg/dL (< 1.67 mmol/L)
Lactate, high	ULN to < 2.0 × ULN without acidosis	≥ 2.0 × ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, high	1.1 to < 1.5 × ULN	1.5 to < 3.0 × ULN	3.0 to < 5.0 × ULN	≥ 5.0 × ULN
Lipid disorder: cholesterol (fasting), high: ≥ 18 years of age	200 to < 240 mg/dL (5.18 to < 6.19 mmol/L)	240 to < 300 mg/dL (6.19 to < 7.77 mmol/L)	≥ 300 mg/dL (≥ 7.77 mmol/L)	—
Lipid disorder: cholesterol (fasting), high: < 18 years of age	170 to < 200 mg/dL (4.40 to < 5.15 mmol/L)	200 to < 300 mg/dL (5.15 to < 7.77 mmol/L)	≥ 300 mg/dL (≥ 7.77 mmol/L)	—
Lipid disorder: LDL (fasting), high: ≥ 18 years of age	130 to < 160 mg/dL (3.37 to < 4.12 mmol/L)	160 to < 190 mg/dL (4.12 to < 4.90 mmol/L)	≥ 190 mg/dL (≥ 4.90 mmol/L)	—
Lipid disorder: LDL (fasting), high: > 2 to < 18 years of age	110 to < 130 mg/dL (2.85 to < 3.34 mmol/L)	130 to < 190 mg/dL (3.34 to < 4.90 mmol/L)	≥ 190 mg/dL (≥ 4.90 mmol/L)	—

ULN = upper limit of normal.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Chemistries (cont.)				
Lipid disorder: triglycerides (fasting), high	150 to 300 mg/dL (1.71 to 3.42 mmol/L)	>300 to 500 mg/dL (>3.42 to 5.7 mmol/L)	>500 to <1,000 mg/dL (>5.7 to 11.4 mmol/L)	>1,000 mg/dL (>11.4 mmol/L)
Magnesium, low	1.2 to <1.4 mEq/L (0.60 to <0.70 mmol/L)	0.9 to <1.2 mEq/L (0.45 to <0.60 mmol/L)	0.6 to <0.9 mEq/L (0.30 to <0.45 mmol/L)	<0.6 mEq/L (<0.30 mmol/L)
Phosphate, low: >14 years of age	2.0 mg/dL to <LLN (0.65 mmol/L to <LLN)	1.4 to <2.0 mg/dL (0.45 to <0.65 mmol/L)	1.0 to <1.4 mg/dL (0.32 to <0.45 mmol/L)	<1.0 mg/dL (<0.32 mmol/L)
Phosphate, low: 1 to 14 years of age	3.0 to <3.5 mg/dL (0.97 to <1.13 mmol/L)	2.5 to <3.0 mg/dL (0.81 to <0.97 mmol/L)	1.5 to <2.5 mg/dL (0.48 to <0.81 mmol/L)	<1.5 mg/dL (<0.48 mmol/L)
Phosphate, low: <1 year of age	3.5 to <4.5 mg/dL (1.13 to <1.45 mmol/L)	2.5 to <3.5 mg/dL (0.81 to <1.13 mmol/L)	1.5 to <2.5 mg/dL (0.48 to <0.81 mmol/L)	<1.5 mg/dL (<0.48 mmol/L)
Potassium, high	5.6 to <6.0 mEq/L or mmol/L	6.0 to <6.5 mEq/L or mmol/L	6.5 to <7.0 mEq/L or mmol/L	≥7.0 mEq/L or mmol/L
Potassium, low	3.0 to <3.4 mEq/L or mmol/L	2.5 to <3.0 mEq/L or mmol/L	2.0 to <2.5 mEq/L or mmol/L	<2.0 mEq/L or mmol/L
Sodium, high	146 to <150 mEq/L or mmol/L	150 to <154 mEq/L or mmol/L	154 to <160 mEq/L or mmol/L	≥160 mEq/L or mmol/L
Sodium, low	130 to <135 mEq/L or mmol/L	125 to <130 mEq/L or mmol/L	121 to <125 mEq/L or mmol/L	<121 mEq/L or mmol/L
Uric acid, high	7.5 to <10.0 mg/dL (0.45 to <0.59 mmol/L)	10.0 to <12.0 mg/dL (0.59 to <0.71 mmol/L)	12.0 to <15.0 mg/dL (0.71 to <0.89 mmol/L)	≥15.0 mg/dL (≥0.89 mmol/L)

LLN = lower limit of normal.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology				
Absolute $CD4^+$ count, low (not HIV infected): >5 years of age	300 to <400 cells/mm^3 (0.300×10^9 to $<0.400 \times 10^9$ cells/L)	200 to <300 cells/mm^3 (0.200×10^9 to $<0.300 \times 10^9$ cells/L)	100 to <200 cells/mm^3 (0.100×10^9 to $<0.200 \times 10^9$ cells/L)	<100 cells/mm^3 (0.100×10^9 cells/L)
Absolute lymphocyte count, low (not HIV infected): >5 years of age	600 to <650 cells/mm^3 (0.600×10^9 to $<0.650 \times 10^9$ cells/L)	500 to <600 cells/mm^3 (0.500×10^9 to $<0.600 \times 10^9$ cells/L)	350 to <500 cells/mm^3 (0.350×10^9 to $<0.500 \times 10^9$ cells/L)	<350 cells/mm^3 ($<0.350 \times 10^9$ cells/L)
Absolute neutrophil count, low: >7 days of age	800 to 1000 cells/mm^3 (0.800×10^9 to 1.000×10^9 cells/L)	600 to 799 cells/mm^3 (0.600×10^9 to 0.799×10^9 cells/L)	400 to 599 cells/mm^3 (0.400×10^9 to 0.599×10^9 cells/L)	<400 cells/mm^3 ($<0.400 \times 10^9$ cells/L)
Absolute neutrophil count, low: 2 to 7 days of age	1250 to 1500 cells/mm^3 (1.250×10^9 to 1.500×10^9 cells/L)	1000 to 1249 cells/mm^3 (1.000×10^9 to 1.249×10^9 cells/L)	750 to 999 cells/mm^3 (0.750×10^9 to 0.999×10^9 cells/L)	<750 cells/mm^3 ($<0.750 \times 10^9$ cells/L)
Absolute neutrophil count, low: ≤1 day of age	4000 to 5000 cells/mm^3 (4.000×10^9 to 5.000×10^9 cells/L)	3000 to 3999 cells/mm^3 (3.000×10^9 to 3.999×10^9 cells/L)	1500 to 2999 cells/mm^3 (1.500×10^9 to 2.999×10^9 cells/L)	<1500 cells/mm^3 ($<1.500 \times 10^9$ cells/L)
Fibrinogen, decreased	100 to <200 mg/dL (1.00 to <2.00 g/L) or 0.75 to $<1.00 \times$ LLN	75 to <100 mg/dL (0.75 to <1.00 g/L) or ≥0.50 to $<0.75 \times$ LLN	50 to <75 mg/dL (0.50 to <0.75 g/L) or 0.25 to $<0.50 \times$ LLN	<50 mg/dL (<0.50 g/L) or $<0.25 \times$ LLN or associated with gross bleeding

LLN = lower limit of normal.

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology (cont.)				
Hemoglobin, low: ≥ 13 years of age (male only) [k]	10.0 to 10.9 g/dL (6.19 to 6.76 mmol/L)	9.0 to < 10.0 g/dL (5.57 to < 6.19 mmol/L)	7.0 to < 9.0 g/dL (4.34 to < 5.57 mmol/L)	< 7.0 g/dL (< 4.34 mmol/L)
Hemoglobin, low: ≥ 13 years of age (female only) [k]	9.5 to 10.4 g/dL (5.88 to 6.48 mmol/L)	8.5 to < 9.5 g/dL (5.25 to < 5.88 mmol/L)	6.5 to < 8.5 g/dL (4.03 to < 5.25 mmol/L)	< 6.5 g/dL (< 4.03 mmol/L)
Hemoglobin, low: 57 days to < 13 years of age (male and female) [k]	9.5 to 10.4 g/dL (5.88 to 6.48 mmol/L)	8.5 to < 9.5 g/dL (5.25 to < 5.88 mmol/L)	6.5 to < 8.5 g/dL (4.03 to < 5.25 mmol/L)	< 6.5 g/dL (< 4.03 mmol/L)
Hemoglobin, low: 36 to 56 days of age (male and female) [k]	8.5 to 9.6 g/dL (5.26 to 5.99 mmol/L)	7.0 to < 8.5 g/dL (4.32 to < 5.26 mmol/L)	6.0 to < 7.0 g/dL (3.72 to < 4.32 mmol/L)	< 6.0 g/dL (< 3.72 mmol/L)
Hemoglobin, low: 22 to 35 days of age (male and female) [k]	9.5 to 11.0 g/dL (5.88 to 6.86 mmol/L)	8.0 to < 9.5 g/dL (4.94 to < 5.88 mmol/L)	6.7 to < 8.0 g/dL (4.15 to < 4.94 mmol/L)	< 6.7 g/dL (< 4.15 mmol/L)
Hemoglobin, low: 8 to ≤ 21 days of age (male and female) [k]	11.0 to 13.0 g/dL (6.81 to 8.10 mmol/L)	9.0 to < 11.0 g/dL (5.57 to < 6.81 mmol/L)	8.0 to < 9.0 g/dL (4.96 to < 5.57 mmol/L)	< 8.0 g/dL (< 4.96 mmol/L)
Hemoglobin, low: ≤ 7 days of age (male and female) [k]	13.0 to 14.0 g/dL (8.05 to 8.72 mmol/L)	10.0 to < 13.0 g/dL (6.19 to < 8.05 mmol/L)	9.0 to < 10.0 g/dL (5.59 to < 6.19 mmol/L)	< 9.0 g/dL (< 5.59 mmol/L)

[k] Male and female sex are defined as sex at birth. For transgender participants ≥ 13 years of age who have been on hormone therapy for more than 6 consecutive months, hemoglobin grade should be based on values for the gender with which they identify (e.g., grade for a transgender female should be based on hemoglobin laboratory values for females).

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Hematology (cont.)				
INR, high (not on anticoagulation therapy)	1.1 to $<1.5\times$ ULN	1.5 to $<2.0\times$ ULN	2.0 to $<3.0\times$ ULN	$\geq 3.0\times$ ULN
Methemoglobin (% hemoglobin)	5.0% to $<10.0\%$	10.0% to $<15.0\%$	15.0% to $<20.0\%$	$\geq 20.0\%$
PTT, high (not on anticoagulation therapy)	1.1 to $<1.66\times$ ULN	1.66 to $<2.33\times$ ULN	2.33 to $<3.00\times$ ULN	$\geq 3.00\times$ ULN
Platelets, decreased	100,000 to $<125{,}000$ cells/mm^3 (100.000×10^9 to $<125.000\times10^9$ cells/L)	50,000 to $<100{,}000$ cells/mm^3 (50.000×10^9 to $<100.000\times10^9$ cells/L)	25,000 to $<50{,}000$ cells/mm^3 (25.000×10^9 to $<50.000\times10^9$ cells/L)	$<25{,}000$ cells/mm^3 ($<25.000\times10^9$ cells/L)
PT, high (not on anticoagulation therapy	1.1 to $<1.25\times$ ULN	1.25 to $<1.50\times$ ULN	1.50 to $<3.00\times$ ULN	$\geq 3.00\times$ ULN
WBC, decreased: >7 days of age	2000 to 2499 cells/mm^3 (2.000×10^9 to 2.499×10^9 cells/L)	1500 to 1999 cells/mm^3 (1.500×10^9 to 1.999×10^9 cells/L)	1000 to 1499 cells/mm^3 (1.000×10^9 to 1.499×10^9 cells/L)	<1000 cells/mm^3 ($<1.000\times10^9$ cells/L)
WBC, decreased: ≤ 7 days of age	5500 to 6999 (5.500×10^9 to 6.999×10^9 cells/L)	4000 to 5499 (4.000×10^9 to 5.499×10^9 cells/L)	2500 to 3999 (2.500×10^9 to 3.999×10^9 cells/L)	<2500 ($<2.500\times10^9$ cells/L)

ULN = upper limit of normal.

Appendix 8: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Urinalysis				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	—
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots or with RBC casts or intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	—

Table 2 Severity Grading for Events Not Specifically Listed in Table 1

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Appendix 9
Investigational, Auxiliary, and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational and Auxiliary Medicinal Product Designations for use in European Economic Area

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
Astegolimab (RO7187807)	*IMP (test product)*	*Not Approved*	*Not applicable*
Astegolimab (RO7187807) placebo	*IMP (placebo)*	*Not approved*	*Not applicable*
LABA	*AxMP (background therapy/standard of care)*	*Approved*	*YES*
SABA [a]	*AxMP (background therapy/standard of care)*	*Approved*	*YES*
LAMA	*AxMP (background therapy/standard of care)*	*Approved*	*YES*
SAMA	*AxMP (background therapy/standard of care)*	*Approved*	*YES*
ICS	*AxMP (background therapy/standard of care)*	*Approved*	*YES*
CS (oral, IV, IM)	*AxMP (background therapy/standard of care)*	*Approved*	*YES*

AxMP =auxiliary medicinal product; CS =corticosteroid; EEA =European Economic Area; ICS =inhaled corticosteroid; IM =intramuscular; IMP =investigational medicinal product; LABA =long-acting beta-agonist; LAMA =long-acting muscarinic antagonist; SABA =short-acting beta-agonist; SAMA =short-acting muscarinic antagonist.

[a] *Includes albuterol/ipratropium.*

Table 2 Investigational and Non-Investigational Medicinal Product Designations for use in the United Kingdom

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in the U.K.*	*Used within Marketing Authorization*
Astegolimab (RO7187807)	*IMP (test product)*	*Not approved*	*Not applicable*
Astegolimab (RO7187807) placebo	*IMP (placebo)*	*Not approved*	*Not applicable*
LABA	*NIMP (background therapy/standard of care)*	*Approved*	*YES*
SABA [a]	*NIMP (background therapy/standard of care)*	*Approved*	*YES*
LAMA	*NIMP (background therapy/standard of care)*	*Approved*	*YES*
SAMA	*NIMP (background therapy/standard of care)*	*Approved*	*YES*
ICS	*NIMP (background therapy/standard of care)*	*Approved*	*YES*
CS (oral, IV, IM)	*NIMP (background therapy/standard of care)*	*Approved*	*YES*

CS =corticosteroid; ICS =inhaled corticosteroid; IM =intramuscular; IMP =investigational medicinal product; LABA =long-acting beta-agonist; LAMA =long-acting muscarinic antagonist; NIMP =non-investigational medicinal product; SABA =short-acting beta-agonist; SAMA =short-acting muscarinic antagonist; U.K. =United Kingdom.

[a] *Includes albuterol/ipratropium.*

Signature Page for Protocol - GB43311 - ASTEGOLIMAB - v4 - Published
System identifier: RIM-CLIN-508727

Approval Task	[redacted] Company Signatory 27-Oct-2023 18:18:04 GMT+0000