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

NCT Number: NCT05595642

Document Date: Protocol Amendment Version 5: 08-Nov-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ASTEGOLIMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**
PROTOCOL NUMBER:	GB44332
STUDY NAME:	ARNASA
VERSION NUMBER:	*5*
TEST COMPOUND:	Astegolimab (RO7187807)
STUDY PHASE:	Phase III
EU TRIAL NUMBER:	2022-502234-70-00
IND NUMBER:	129,714
NCT NUMBER:	NCT05595642
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 *4058* Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	See electronic date stamp on final page.
4	20 June 2023
3	26 May 2023
2	9 November 2022
1	16 September 2022

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

GB44332 has been amended to include the extended Japan enrollment phase into the end of study definition. Furthermore, the protocol section on statistical considerations was aligned with the currently planned statistical analyses, and the country-specific protocol (China) was integrated into this global protocol version. Finally, several local and global protocol clarification letters and non-substantial amendments to the previous protocol version were integrated. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- Following further development of the planned statistical analysis methods, updates were made to the statistical considerations section of the protocol. Substantive updates include addition of a new secondary estimand for annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period in individuals who have a blood eosinophil level $<$ 300 cells/µL, changes to the intercurrent events definition / handling and additional sensitivity analyses (Section 1.3 [Table 1], Section 3 [Table 3], Section 9.3.2.1, and Section 9.3.2.3).
- Protocol clarifications and non-substantial amendments to the previous protocol version were integrated (Section 1.3 [Table 1], Section 5.2, Section 8.4.3, Section 8.5.1).
- A new section was added which lists all previously agreed country-specific stipulations (Section 4.1.1).
- A rationale for collection of race and ethnicity data was included (Section 4.2.4).
- The extended Japan enrollment phase was added to the end of study definition, in order that the definition encompasses the global, extended China and extended Japan enrollment phases (Section 4.4).
- Clarification was added regarding the expedited safety reporting requirements for hypersensitivity reactions (Section 8.5.8).
- The process for reporting medical product complaints was clarified (Appendix 6).
- The appendix for investigational medicinal product (IMP) and auxiliary medicinal product (AxMP) / non-investigational medicinal product (NIMP) designations was separated into EEA and UK appendices. Non-exhaustive lists of example products for the classes of medicines used as AxMP / NIMP were added as per the Sponsor's current practice (Appendix 11 and Appendix 12).
- An appendix was added as per local regulations which describes the domestic companies used for central laboratory testing, analysis, and sample destruction of samples collected from participants from China (Appendix 13).

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

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ASTEGOLIMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**
PROTOCOL NUMBER:	GB44332
STUDY NAME:	ARNASA
VERSION NUMBER:	*5*
TEST COMPOUND:	Astegolimab (RO7187807)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

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 Contract Research Organization (CRO).

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ASTEGOLIMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 129,714 EU Trial Number: 2022-002705-23502234-70-00 NCT Number: NCT05595642

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of astegolimab compared with placebo in participants with chronic obstructive pulmonary disease (COPD) who are former or current smokers and have a history of frequent exacerbations.

OBJECTIVES AND ENDPOINTS

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (FDA 2020) in Section 3.

Primary Objective	Estimand Definition
• To evaluate the efficacy of astegolimab compared with placebo	• Population: *individuals* with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period – A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) that lead to treatment (duration $\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 • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – Use of prohibited medications for management of COPD exacerbation *risk that leads to treatment discontinuation: the event will be classified as a "moderate COPD exacerbation" under the composite strategy. Additionally, since patients may continue in the study after the treatment discontinuation, all subsequent measurements after the prohibited medication use will be censored (hypothetical strategy).* – *Treatment discontinuation not due to the use of prohibited medications for management of COPD*

	exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy) – Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication *other than the ones* for management of COPD exacerbation risk *and leading to treatment discontinuation*. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy). – Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy). • Population-level summary: RR for annualized rate of moderate and severe COPD exacerbations

Secondary Objectives	Estimand Definition
• *To evaluate the efficacy of astegolimab compared with placebo*	• *Population: individuals with COPD who are former or current smokers, have a history of frequent exacerbations and have a blood eosinophil level <300 cells/µL.* • *Endpoint: annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period.* – *A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) that lead to treatment (duration ≥3 days) with systemic corticosteroids (oral, IV, or IM) at a dose of >10 mg/day prednisolone equivalent and/or antibiotics.* – *A severe COPD exacerbation is defined as new or increased COPD symptoms that lead to hospitalization (duration >24 hours) or lead to death.* • *Treatment:* – *Experimental: astegolimab 476 mg SC Q2W* – *Experimental: astegolimab 476 mg SC Q4W* – *Control: placebo SC Q2W* • *Intercurrent events and handling strategies:* – *Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: the event will be classified as a "moderate COPD exacerbation" under the composite strategy. Additionally, since patients may continue in the study after the treatment discontinuation, all subsequent measurements after the prohibited medication use will be censored (hypothetical strategy).*

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

	all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy). – *Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy).* • Population-level summary: HR for time to first COPD exacerbation
• To evaluate the efficacy of astegolimab compared with placebo	• Population: *individuals* with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: – Absolute change from baseline in HRQoL at Week 52, as assessed through the SGRQ-C total score – Absolute change from baseline in post-bronchodilator FEV_1 (liters) at Week 52 – Absolute change from baseline in E-RS:COPD total score at Week 52 • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – *Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: under the composite strategy, since patients may continue in the study after the treatment discontinuation, all subsequent measurements after the use of prohibited medication will be imputed with a conservative value, assuming treatment failure for COPD.* – *Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy).* – *Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy).* – *Death not related to COPD exacerbation: Data will be censored after the death occurrence (i.e., hypothetical strategy).* • Population-level summary: difference in mean absolute change at Week 52

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

	study after the treatment discontinuation, all subsequent measurements after event will be censored (hypothetical strategy). – *Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy).* – *Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy).* – *Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy).* • Population-level summary: RR for annualized rate of severe COPD exacerbations

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

OVERALL DESIGN

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of astegolimab in combination with standard of care (SOC) compared with placebo in combination with SOC, in participants with COPD who are former or current smokers and have a history of frequent exacerbations. Approximately 1290 participants with COPD are expected to be enrolled globally.

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

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

- Astegolimab 476 mg SC every 2 weeks (Q2W)
- Astegolimab 476 mg SC every 4 weeks (Q4W)

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

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

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

Phase:	Phase 3	**Population Type:**	Adult patients of any gender
Control Method:	Placebo	**Population Diagnosis or Condition:**	Chronic obstructive pulmonary disease
Interventional Model:	Parallel group	**Population Age:**	40–80 years
Test Compound{s}:	Astegolimab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	3	**Number of Participants to Be Enrolled:**	Approximately 1290 participants

STUDY TREATMENT

Astegolimab and placebo will be supplied by the Sponsor as a sterile liquid in [redacted]

For information on the astegolimab and placebo formulation, see the pharmacy manual and/or Astegolimab Investigator's Brochure.

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 [redacted] See the pharmacy manual for details on study drug preparation and administration.

All participants 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 participant develops any signs or symptoms to suggest a systemic hypersensitivity reaction or anaphylactic event, longer observation may be warranted as per 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.

DURATION OF PARTICIPATION

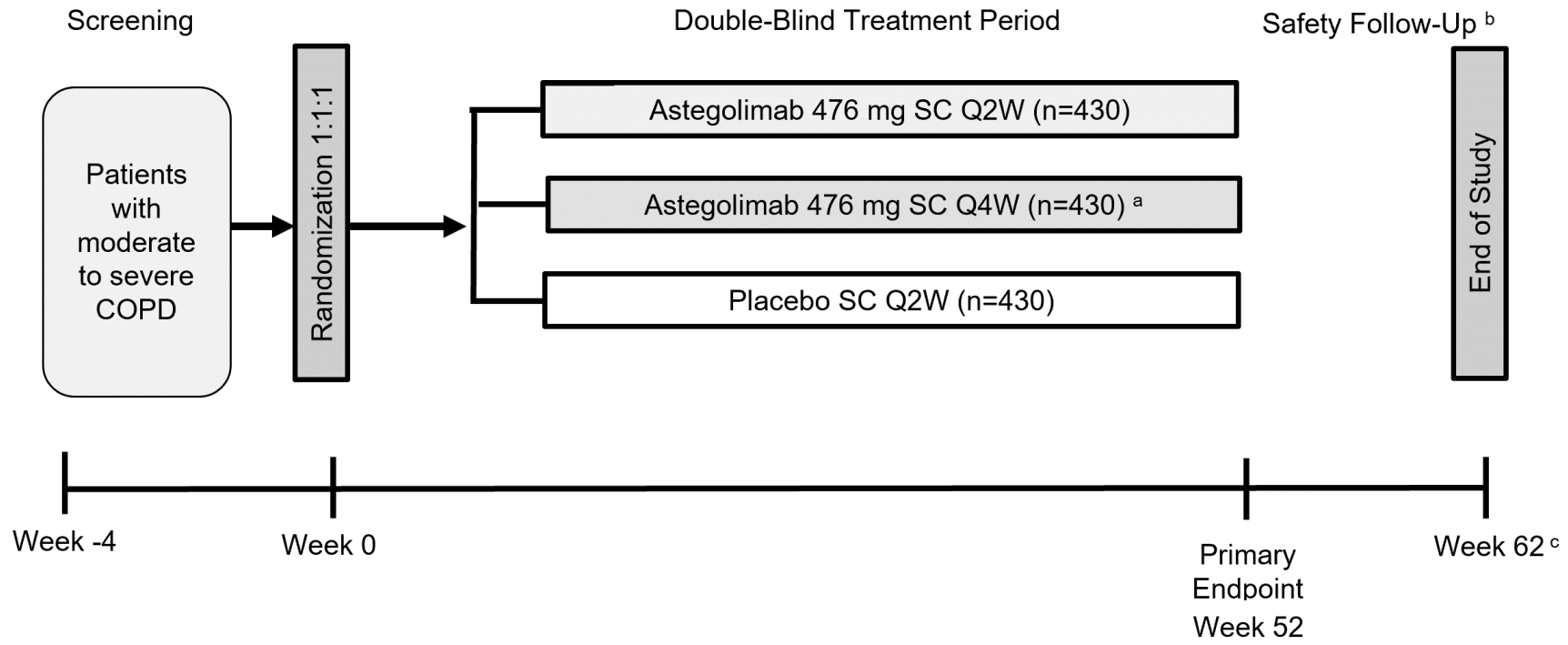
The total duration of study participation for each individual is expected to be approximately 15 months.

COMMITTEES

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

1.2 STUDY SCHEMA

Figure 1 Study Schema



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

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

[b] Participants will enter the safety follow-up period and undergo end of study assessments 12 weeks after their last dose of study drug, as detailed in Section 4.1.3.

[c] Participants enrolled in this study may have the opportunity to participate in OLE Study GB43374, if eligible, as detailed in Section 4.1.2.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Visit (V)	Protocol Reference	Screen [a]	Treatment Period									Treat Compl/ Disc [b]	EOS/ Safety Follow-Up [b]
		V1	V2 (Day 1)	V3–V7 [c, d, e] (every 2 wk)	V8	V9–V13 [c, d, e] (every 2 wk)	V14	V15–V19 [c, d, e] (every 2 wk)	V20	V21–26 [c, d, e] (every 2 wk)	V27 [e]	V28	V29
Week		–4 to –1	0	2–10	12	14–22	24	26–34	36	38–48	50	52	62
(Window)				(±3 days)									(±7 days)
Informed consent	8.1	x											
Demographic data	8.2	x											
Medical history and baseline conditions	8.2	x											
Smoking history	8.2.1	x	x		x		x		x			x	x
Smoking cessation counseling [f]	8.2.2	x											
Vital signs	8.4.2	x	x	x	x	x	x	x	x	x	x	x	x
Height	–	x											
Weight	–	x										x	
Complete physical examination	8.4.1	x											
Limited physical examination	8.4.1		x		x		x		x			x	x
Chest X-ray [g]	8.2.3	x											

Table 1: Schedule of Activities (cont.)

Visit (V)	Protocol Reference	Screen [a]	Treatment Period									Treat Compl/ Disc [b]	EOS/ Safety Follow-Up [b]
		V1	V2 (Day 1)	V3–V7 [c, d, e] (every 2 wk)	V8	V9–V13 [c, d, e] (every 2 wk)	V14	V15–V19 [c, d, e] (every 2 wk)	V20	V21–26 [c, d, e] (every 2 wk)	V27 [e]	V28	V29
Week		–4 to –1	0	2–10	12	14–22	24	26–34	36	38–48	50	52	62
(Window)				(±3 days)									(±7 days)
SGRQ-C	8.3.3.1 A7–2		x		x		x		x			x	
mMRC	8.3.3.2 A7–4	x	x				x					x	
EQ-5D-5L	8.3.3.4		x		x		x		x			x	
eDiary [h] (EXACT®, E-RS®:COPD)	8.3.3.3 *A7–3*		x		x		x		x			x	
Single ECG	8.4.3	x	x		x		x		x			x	x
Pre-bronchodilator spirometry [i]	8.3.2.1		x									x	
Post-bronchodilator spirometry [i]	8.3.2.2	x	x		x		x		x			x	
Concomitant medications	6.8	x	x	x	x	x	x	x	x	x	x	x	x

Table 1: Schedule of Activities (cont.)

Visit (V)	Protocol Reference	Screen [a]	Treatment Period									Treat Compl/ Disc [b]	EOS/ Safety Follow-Up [b]
		V1	V2 (Day 1)	V3–V7 [c, d, e] (every 2 wk)	V8	V9–V13 [c, d, e] (every 2 wk)	V14	V15–V19 [c, d, e] (every 2 wk)	V20	V21–26 [c, d, e] (every 2 wk)	V27 [e]	V28	V29
Week		–4 to –1	0	2–10	12	14–22	24	26–34	36	38–48	50	52	62
(Window)				(±3 days)									(±7 days)
Adverse events	8.5 Appendix 3 Appendix 4		x	x	x	x	x	x	x	x	x	x	x
COPD exacerbation assessment	8.3.1		x	x	x	x	x	x	x	x	x	x	x
Adherence with background COPD treatment	–	x	x	x	x	x	x	x	x	x	x	x	
Chemistry	Appendix 2	x	x	Weeks 4 and 8 only	x		x		x			x	x
Hematology	Appendix 2	x	x	Weeks 4 and 8 only	x		x		x			x	x
HIV and/or TB testing [j]	4.1.1 5.2	x											
Urinalysis	Appendix 2	x											

Table 1: Schedule of Activities (cont.)

Visit (V)	Protocol Reference	Screen [a]	Treatment Period									Treat Compl/ Disc [b]	EOS/ Safety Follow-Up [b]
		V1	V2 (Day 1)	V3–V7 [c, d, e] (every 2 wk)	V8	V9–V13 [c, d, e] (every 2 wk)	V14	V15–V19 [c, d, e] (every 2 wk)	V20	V21–26 [c, d, e] (every 2 wk)	V27 [e]	V28	V29
Week		–4 to –1	0	2–10	12	14–22	24	26–34	36	38–48	50	52	62
(Window)				(±3 days)									(±7 days)
Pregnancy Test (WOCBP) [k]	8.4.5 Appendix 2	x	x	x	x	x	x	x	x	x	x	x	x
Serum PK sample [l]	8.6		x	Week 4 only	x		x		x			x	x
Serum ADA sample	8.10		x	Week 4 only	x		x		x			x	x
Serum samples for biomarkers [l]	8.9		x	Week 4 only	x		x		x			x	x
Plasma samples for biomarkers *(not applicable in China)*	8.9		x	Week 4 only	x		x		x			x	x
Blood sample for specified DNA SNP analysis (mandatory)	8.9		x										

Table 1: Schedule of Activities (cont.)

Visit (V)	Protocol Reference	Screen [a]	Treatment Period									Treat Compl/ Disc [b]	EOS/ Safety Follow-Up [b]
		V1	V2 (Day 1)	V3–V7 [c, d, e] (every 2 wk)	V8	V9–V13 [c, d, e] (every 2 wk)	V14	V15–V19 [c, d, e] (every 2 wk)	V20	V21–26 [c, d, e] (every 2 wk)	V27 [e]	V28	V29
Week		**–4 to –1**	**0**	**2–10**	**12**	**14–22**	**24**	**26–34**	**36**	**38–48**	**50**	**52**	**62**
(Window)				**(±3 days)**									**(±7 days)**
Blood sample for RBR (optional) [m]	8.11.2		x										
Study drug administration [n]	6.1		x	x	x	x	x	x	x	x	x		
Physical Activity Monitoring (For consenting participants at participating sites only) [o]													
Physical activity measure	8.11.1		x		x		x					x	
Physical activity monitor dispensation	8.11.1	x		Week 10		Week 22					x		

ADA = anti-drug antibody; Compl = completion; COPD = chronic obstructive pulmonary disease; CT = computed tomography; 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; FEV = forced expiratory volume; FVC = forced vital capacity; mmRC = modified Medical Research Council Dyspnea Scale; OLE = open-label extension; PK = pharmacokinetic; PRO = participant-reported outcome; RBR = Research Biosample Repository; Screen = screening; SGRQ-C = St. George's Respiratory Questionnaire-COPD; SNP = single nucleotide polymorphism; TB = tuberculosis; V = visit; 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] A minimum screening period of 7 days prior to randomization is required. See Section 5.4.

Table 1: Schedule of Activities (cont.)

[b] See Section 4.1.3.

[c] 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.).

[d] For participants 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 participant's home or another suitable location.

[e] For participants 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.

[f] For participants who are current smokers.

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

[h] eDiary training and/or distribution must be performed prior to the specified timepoints, to allow completion of the diary for 7 days.

[i] *For Visit 2 and Visit 28, participants must withhold inhaled bronchodilators until pre-bronchodilator spirometry measurements are completed as per Section 8.3.2.1.*

[j] HIV and/or TB testing conducted where required by local regulations. HIV and/or TB testing does not need to be repeated if performed within 3 months prior to screening. *Patients with a positive tuberculosis test result at screening that have completed adequate treatment as per local guidelines do not need to be retested. For South Africa, additional TB testing after initiation of study treatment should be performed as locally required (see Section 4.1.1).*

[k] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed locally at subsequent visits prior to study drug administration. 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 test result must be confirmed by a serum pregnancy test. See Section 8.5.5 for reporting requirements for a participant with a positive pregnancy test.

[l] For approximately the first 60 patients enrolled in mainland China, additional PK and biomarker assessments are required as per Table 2.

[m] The RBR sample is optional and should only be obtained from participants who sign the separate RBR ICF. Not applicable for a site that has not been granted approval for RBR sampling.

[n] A minimum 8-day interval between study drug administrations is required (see Section 6.1 for details).

[o] 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 participants, and data collection will be provided.

Table 2 Schedule of Intensive Pharmacokinetic and Pharmacodynamic Biomarker Sampling for Patients in Mainland China

Visit (V) [a]	Timepoint [b]	Sample Type
2-a	3 days after V2 (±1 day)	• Serum PK and biomarker sample
2-b	7 days after V2 (±1 day)	• Serum PK and biomarker sample
2-c	10 days after V2 (±1 day)	• Serum PK and biomarker sample
26	V26 (see Table 1)	• Serum PK and biomarker sample
26-a	7 days after V26 (±1 day)	• Serum PK and biomarker sample
28-a [c]	28 days after V28 (±14 days)	• Serum PK and biomarker sample

COPD = chronic obstructive pulmonary disease; OLE = open-label extension; PK = pharmacokinetic; V = visit.

Notes: Intensive PK and biomarker samples will be collected in early enrolled patients in mainland China, targeting approximately 60 patients. Once sufficient numbers of participants are enrolled, subsequent participants in mainland China will follow the PK schedule as specified in Table 1. Intensive PK samples are in addition to the standard PK samples specified in Table 1. PK and biomarker samples are to be collected prior to dosing, when applicable, and at approximately the same time each day. For patients at participating sites who have provided written informed consent to participate in mobile nursing visits, visits may be performed by a trained nursing professional at the patient's home or another suitable location.

[a] PK and biomarker 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 Table 1.

[b] Visit windows should be calculated in relation to the first dosing day (Day 1 of Week 0 [V2]).

[c] For patients enrolling in OLE Study GB43374, Visit 28-a should not be conducted.

2. BACKGROUND

2.1 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 (World Health Organization [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 COPD usually occurs in patients aged 40 years or older; the prevalence is greater among men than women (Landis et al. 2014).

Chronic obstructive pulmonary disease is characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar abnormalities (Global Initiative for Chronic Obstructive Lung Disease [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. Chronic obstructive pulmonary disease is a heterogeneous and progressive disease, with progression being strongly associated with airway-wall thickening and airflow limitation. The 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 frequency of COPD exacerbations is associated with a 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 risk of future exacerbations (Hurst et al. 2010). Chronic obstructive pulmonary disease exacerbations are not only a major cause of morbidity and mortality, but also account for the greatest proportion of 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 (β-agonists and anticholinergics), inhaled and systemic corticosteroids, azithromycin, and phosphodiesterase inhibitors (GOLD 2021). Despite these treatment options, slowing 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 symptoms in patients and alter the disease trajectory are urgently needed (Cazzola et al. 2016).

2.2 BACKGROUND ON ASTEGOLIMAB

Astegolimab (also known as RO7187807 or MSTT1041A) is a fully human, IgG2 monoclonal antibody that binds with high affinity to the interleukin (IL)-33 (IL-33) receptor, ST2, thereby blocking the signaling of IL-33, an inflammatory cytokine of the 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.

2.3 BACKGROUND ON INTERLEUKIN-33 AND ST2

Interleukin-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 exogenous stimuli such as allergens, toxins, or infections. Interleukin-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). Interleukin-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.

Interleukin-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.

Interleukin-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 hyper responsiveness (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 IL-5, IL-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. Interleukin-33 release can trigger acute exacerbations and/or disease progression in asthma, COPD, idiopathic pulmonary fibrosis, and acute respiratory distress syndrome. Interleukin-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). Mice deficient in ST2 or IL-33 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.

2.3.1 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.

2.3.2 Summary of Clinical Studies

As of the data cutoff of 15 February 2024, 653 patients with asthma (Study GB39242), 2033 patients with COPD (1952/2033 from the ongoing/blinded Studies GB43311 and GB44332), 1 patient with chronic rhinosinusitis with nasal polyps (Amgen Study 20110236), 410 patients with severe coronavirus disease 2019 (COVID-19) pneumonia (Study GA42469), 65 patients with atopic dermatitis (Study GS40965), and 145 healthy subjects (Amgen Studies 20110235, 20110236, and 20130177) have been enrolled into astegolimab clinical studies.

A total of approximately 583 patients and 109 healthy subjects have been exposed to at least 1 dose of astegolimab in the completed studies.

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

2.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Chronic obstructive pulmonary disease is recognized as a progressive, heterogeneous disease. Chronic obstructive pulmonary disease 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.

Chronic obstructive pulmonary disease exacerbations can be attributed to a variety of underlying factors, including bacterial, viral, eosinophilic, or pollution-related. As detailed in Section 2.2, 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 IL-33/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 IL-33/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 1 ongoing or 6 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%–27% (in the 5 completed clinical studies in which anti-drug antibody [ADA] data is 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 mouse 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 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 participants 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 participants with COPD.

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.

Detailed information on astegolimab is provided in the Astegolimab Investigator's Brochure.

See Appendix 4 for information on anticipated risks for astegolimab and risk mitigation measures, including guidelines for managing adverse events associated with astegolimab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of astegolimab may be found in the Astegolimab Investigator's Brochure.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This study will evaluate the efficacy and safety astegolimab compared with placebo in participants with COPD who are former or current smokers and have a history of frequent exacerbations. Table 3 presents the primary and secondary objectives for the study expressed using the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials (U.S. Food and Drug Administration [FDA] 2020). Table 4 presents the remaining objectives and corresponding endpoints.

Table 3 Primary and Secondary Objectives and Corresponding Estimands

Primary Objective	Estimand Definition
• To evaluate the efficacy of astegolimab compared with placebo	• Population: *individuals* with COPD who are former or current smokers and have a history of frequent exacerbations

Table 3 Primary and Secondary Objectives and Corresponding Estimands (cont.)

Primary Objective	Estimand Definition
	• Endpoint: annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period – A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) that lead to treatment (duration ≥3 days) with systemic corticosteroids (oral, IV, or IM) at a dose of >10 mg/day prednisolone equivalent and/or antibiotics – A severe COPD exacerbation is defined as new or increased COPD symptoms that lead to hospitalization (duration >24 hours) or lead to death • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – Use of prohibited medications for management of COPD exacerbation *risk that leads to treatment discontinuation: the event will be classified as a "moderate COPD exacerbation" under the composite strategy. Additionally, since patients may continue in the study after the treatment discontinuation, all subsequent measurements after the prohibited medication use will be censored (hypothetical strategy).* – *Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy)* – Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication *other than the ones* for management of COPD exacerbation risk *and leading to treatment discontinuation*. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy). – Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy). • Population-level summary: RR for annualized rate of moderate and severe COPD exacerbations

Table 3 Primary and Secondary Objectives and Corresponding Estimands (cont.)

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

Table 3 Primary and Secondary Objectives and Corresponding Estimands (cont.)

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

Table 3 Primary and Secondary Objectives and Corresponding Estimands (cont.)

Secondary Objectives	Estimand Definition
• To evaluate the efficacy of astegolimab compared with placebo	• Population: *individuals* with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: – Absolute change from baseline in HRQoL at Week 52, as assessed through the SGRQ-C total score – Absolute change from baseline in post-bronchodilator FEV_1 (liters) at Week 52 – Absolute change from baseline in E-RS:COPD total score at Week 52 • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – *Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: under the composite strategy, since patients may continue in the study after the treatment discontinuation, all subsequent measurements after the use of prohibited medication will be imputed with a conservative value, assuming treatment failure for COPD.* – *Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy).* – *Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy).* – *Death not related to COPD exacerbation: Data will be censored after the death occurrence (i.e., hypothetical strategy).* • Population-level summary: difference in mean absolute change at Week 52

Table 3 Primary and Secondary Objectives and Corresponding Estimands (cont.)

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

Table 3 Primary and Secondary Objectives and Corresponding Estimands (cont.)

Secondary Objectives	Estimand Definition
• To evaluate the efficacy of astegolimab compared with placebo	• Population: *individuals* with COPD who are former or current smokers and have a history of frequent exacerbations • Endpoint: annualized rate of severe COPD exacerbations over the 52-week treatment period • Treatment: – Experimental: astegolimab 476 mg SC Q2W – Experimental: astegolimab 476 mg SC Q4W – Control: placebo SC Q2W • Intercurrent events and handling strategies: – *Use of prohibited medications for management of COPD exacerbation risk that leads to treatment discontinuation: patients may continue in the study after the treatment discontinuation, all subsequent measurements after event will be censored (hypothetical strategy).* – *Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy).* – *Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy).* – *Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy).* • Population-level summary: RR for annualized rate of severe COPD exacerbations

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

Table 4 Other Secondary and Exploratory Objectives and Endpoints

Secondary Objectives	Corresponding Endpoints
• To evaluate the safety of astegolimab compared with placebo	• Incidence and severity of all TEAEs, including SAEs, AESIs, and TEAEs leading to death or discontinuation TEAEs severity will be determined according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (HHS 2017) (hereafter referred to as the DAIDS Toxicity Grading Scale), with slight modifications for clarity and for alignment with internal practices (see Appendix 8) • Change from baseline in selected vital signs • Change from baseline in selected clinical laboratory test results and ECGs
• To characterize the astegolimab PK profile	• Serum concentration of astegolimab at specified timepoints
• To evaluate the immune response to astegolimab	• Prevalence of ADAs at baseline and incidence of ADAs during the study
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of astegolimab compared with placebo	• Change in COPD symptoms as measured by the E-RS:COPD total score at Week 24 • Change in E-RS:COPD individual domain scores (breathlessness, cough and sputum, and chest symptoms) from baseline at Week 24 and 52 • Change in EXACT individual domain scores (tired or weak, sleep disturbance, and scared or worried) from baseline at Week 24 and 52 • Proportion of participants with HRQoL improvement, defined as a decrease from baseline of ≥ 4 points in SGRQ-C total score, at Week 12 and Week 24 • Proportion of participants with symptom improvement, defined as a decrease of ≥ 2 points from baseline in E-RS:COPD total score, at Week 24 and Week 52 • Absolute change from baseline in post-bronchodilator FEV_1 (liters) at Weeks 12, 24, and 36 • Annualized rate of moderate COPD exacerbations over the 52-week treatment period • Duration of hospital stay for severe COPD exacerbations • Proportion of severe COPD exacerbations requiring hospital readmission within 30 days • Absolute change from baseline in daily step count at Weeks 12, 24, and 52 • Absolute change from baseline in time in moderate and vigorous physical activity at Weeks 12, 24, and 52 • *Annual change rate of FEV_1 (liters/year)* • *Absolute change from baseline in post-bronchodilator FVC (liters) at Weeks 12, 24, 36, and 52*

Table 4 Other Secondary and Exploratory Objectives and Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
	• *Overall survival, defined as the time from randomization to death from any cause*
• To evaluate potential relationships between drug exposure and the efficacy and safety of astegolimab	• Relationship between serum concentration or PK parameters for astegolimab and efficacy endpoints • Relationship between serum concentration or PK parameters for astegolimab and safety endpoints
• To evaluate potential relationships between selected covariates and exposure to astegolimab	• Relationship between selected covariates and serum concentration or PK parameters for astegolimab
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, PK or biomarker endpoints
• To identify and/or evaluate biomarkers that are predictive of response to astegolimab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of astegolimab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety or pharmacokinetics	• Relationship between biomarkers in blood, plasma, and serum (listed in Section 8.9) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
• To evaluate health status utility scores of participants treated with astegolimab compared with placebo	• Change from baseline in EuroQol EQ-5D-5L index-based and VAS scores at Week 52

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

4. STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of astegolimab in combination with standard of care (SOC; defined in Section 6.1.1) compared with placebo in combination with SOC, in participants with COPD who are former or current smokers and have a history of

frequent exacerbations. Approximately 1290 participants with COPD are expected to be enrolled globally.

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

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

- Astegolimab 476 mg SC every 2 weeks (Q2W)
- Astegolimab 476 mg SC every 4 weeks (Q4W)

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

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

If a separate open-label extension (OLE) study, Study GB43374, is open and available in their respective country, all participants enrolled in this study and who have completed the Week 52 visit will be given the option to either participate in OLE Study GB43374, if eligible (see Section 4.1.2), or enter the safety follow-up period (see Section 4.1.3). If OLE Study GB43374 is not opened, all participants who complete the Week 52 visit, including those participants receiving continued blinded treatment after Week 52, will enter the safety follow-up period. All participants will undergo a safety follow-up visit 12 weeks after their final dose of study drug (regardless of the length of treatment received).

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

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities is provided in Section 1.3 (see Table 1).

4.1.1 *Country-specific Stipulations*

4.1.1.1 *European Union Member States*

Patients must have a negative HIV test result and negative TB test result at screening or within 3 months prior to screening (Section 5.2).

4.1.1.2 *South Africa*

Patients must have a negative HIV test result and TB test result at screening or within 3 months prior to screening (Section 5.2). Furthermore, TB testing needs to be performed approximately every 6 months while receiving study treatment.

4.1.1.3 *China*

For China, collection of plasma samples for biomarkers is not applicable. Furthermore, only the biomarker analyses specified in Appendix 13 will be conducted.

4.1.2 Open-Label Extension Study GB43374

A separate OLE study for Study GB43311 will be opened subject to approval by local Institutional Review Boards (IRBs) or Ethics Committees (ECs) and relevant health authorities. Participants who complete the study treatment period through the Week 52 treatment completion visit 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. Participants 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 4.1.3).

Participants 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 4.1.3).

4.1.3 Safety Follow-Up Period and Assessments after Study Treatment Discontinuation

Participants who complete the study treatment period through the Week 52 treatment completion visit 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.

Participants who discontinue study drug prematurely during the 52-week treatment period 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 participants, telephone visits may replace certain in-clinic visits. Specific details are outlined in Table 1.

Participants who discontinue study drug prematurely during the 52-week treatment period 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.

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

4.1.4 Independent Data Monitoring Committee

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

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

Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective IRBs/ECs.

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

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study 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 2 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 enroll participants with moderate to very severe airflow obstruction who have a history of frequent exacerbations (defined as 2 or more exacerbations in the prior 12 months).

4.2.2 Rationale for Biomarker Assessments

Chronic obstructive pulmonary disease is a heterogeneous disease and IL-33 and sST2 expression has been shown to vary among patients. Therefore, all participants 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 participants, identify biomarkers that may be predictive of response to astegolimab, define pharmacokinetic (PK) and/or pharmacodynamic (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 understating 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., C-reactive protein).

A blood sample will be collected for DNA extraction to enable identification of specific germline mutations in *IL1RL1, IL-33,* 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 participant management.

4.2.3 Rationale for Control Group

The study will compare the efficacy, safety and pharmacokinetics of astegolimab in combination with SOC (defined in Section 6.1.1) compared with placebo in combination with SOC in participants with COPD. Treatment with SOC ensures that all participants receive therapy for COPD; the placebo control group takes into account safety, efficacy, and ethical considerations for studying the effects of astegolimab.

4.2.4 *Rationale for Collection of Information on Race and Ethnicity*

Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial, including identification of potential differences in efficacy, safety, and pharmacokinetics among participants. Collection of race and ethnicity data may enable investigation of potential relationships between biomarkers and race or ethnicity, including determination of whether race or ethnicity could be a

prognostic factor. Collection of these data may also contribute to a better understanding of the distribution of COPD according to race or ethnicity.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

The two astegolimab dosing regimens, 476 mg Q2W and 476 mg Q4W, were selected on the basis of PK, 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 range-finding 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 investigator-initiated study (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 ($p=0.195$). Study GB39242 showed a lack of consistent and clear dose-response and exposure-response relationships for the annual exacerbation rate ratio) and positive dose-response and exposure-response trends 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 3 doses) and 210 mg SC (Q2W for 6 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 supported by nonclinical safety data, 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 the maximum observed 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.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the last visit in the safety follow-up period (see Table 1) or entered into OLE Study GB43374, if eligible (see Section 4.1.2).

The end of this study is defined as the date when the visit of last participant (i.e., last participant in the global, extended China, *and extended Japan* enrollment phases combined) or the date at which the last data point required for statistical analysis (i.e., primary analyses) or safety follow-up is received from the last participant (global, extended China, *and extended Japan* enrollment phases combined), whichever occurs later. The end of the study is expected to occur approximately 15 months after the last participant is enrolled.

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

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 15 months.

5. STUDY POPULATION

Approximately 1290 participants with COPD and a history of frequent exacerbations will be enrolled during the global enrollment phase of this study. After completion of the global enrollment phase, additional participants may be enrolled at China's sites in an extended China enrollment *phase, and at Japan's sites in an extended Japan enrollment phase*.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Able and willing to provide written informed consent and to comply with the study protocol
- Age 40–80 years at Visit 1
- Documented COPD diagnosis for ≥ 12 months prior to Visit 1
- History of frequent exacerbations, defined as having had 2 or more moderate or severe COPD exacerbations within 12 months prior to Visit 1

  A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) that lead to treatment with systemic corticosteroids (oral, IV, or intramuscular [IM]) 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 at Visit 1 or Visit 2
- Post-bronchodilator $FEV_1/FVC < 0.70$ at Visit 1 or Visit 2
- mMRC score ≥ 2 at screening
- Current tobacco smoker (see definition in Section 8.2.2) or former smoker (having stopped smoking for at least 6 months prior to Visit 1) with a history of smoking ≥ 10 pack-years (e.g., 20 cigarettes/day for 10 years)

  At Visit 1, participants who meet the protocol definition of current smoker will receive smoking cessation counseling (see Section 8.2.2)
- On optimized COPD maintenance therapy as defined below for ≥ 12 months prior to Visit 1.
  - Inhaled corticosteroid (ICS) plus long-acting beta-agonist (LABA)
  - Long-acting muscarinic antagonist (LAMA) plus LABA
  - ICS plus LAMA plus LABA

  Participants must be stable on current medications and doses for at least 4 weeks prior to Visit 1.

  Initiation of new COPD therapy, including a methylxanthine preparation, maintenance macrolide therapy, and/or phosphodiesterase 4 (PDE4) inhibitor is not permitted within 4 weeks prior to Visit 1.
- Chest X-ray or computed tomography (CT) scan within 6 months prior to Visit 1 or chest X-ray during the screening period (prior to Visit 2) that confirms the absence of clinically significant lung disease besides COPD
- Demonstrated ability to use and comply with electronic diary (eDiary) requirements, defined as completion of all questions on at least 5 of 7 days prior to Visit 2

  Participants unable to demonstrate compliance with the eDiary during the screening period will be screen failed. Participants will have the opportunity to demonstrate eDiary compliance if re-screened (see Section 8.3.3.3).
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Female participants 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 female participant 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). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. 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 individual. 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 male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, male participants 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. Male participants 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 individual. 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 participants enrolled in the extended China enrollment phase at China's sites: must be current residents of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the study drug
- Any prior treatment with astegolimab
- Current documented diagnosis of asthma
- History of clinically significant pulmonary disease other than COPD

- Diagnosis of $\alpha-1$-antitrypsin deficiency
- History of long-term treatment with oxygen at >4.0 liters/minute

  While breathing supplemental oxygen, the participant should demonstrate an oxyhemoglobin saturation of $\geq 89\%$.
- Lung volume reduction surgery or procedure within 12 months prior to Visit 1
- Individuals participating in, or scheduled for, an intensive COPD rehabilitation program (participants who are in the maintenance phase of a rehabilitation program are eligible)
- History of lung transplant
- Any infection that resulted in hospital admission for ≥ 24 hours and/or treatment with oral, IV, or IM antibiotics within 4 weeks prior to Visit 1 or during screening
- Upper or lower respiratory tract infection within 4 weeks prior to Visit 1 or during screening
- Treatment with oral, IV, or IM corticosteroids (>10 mg/day prednisolone or 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 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)
- Planned surgical intervention during the study
- Receipt of a live attenuated vaccine within 4 weeks prior to Visit 1 or during screening
- 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

  Where required by local regulations: Patients must have a negative tuberculosis test result at screening or within 3 months prior to screening. *Patients with a positive tuberculosis test result at screening that have completed adequate treatment as per local guidelines do not need to be retested.*
- AST, ALT, or total bilirubin elevation $\geq 2.0\times$ the upper limit of normal (ULN) during screening
- 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 participant'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 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) $>$450 ms if the participant is male or QTcF $>$470 ms if the participant is female*, demonstrated by at least two ECGs $>$30 minutes apart*

  For male or female participants 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
- Pregnant or breastfeeding, or intention of becoming pregnant during the study or within 12 weeks after the final dose of astegolimab

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for 2 re-screening opportunities (for a total of 3 screenings per individual) at the investigator's discretion. Participants are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form.
The investigator will maintain a record of reasons for screen failure (see Section 8).

In the event the participant is re-screened, screening assessments should be repeated as follows:

- If the participant 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 the participant 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. The 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.

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The investigational medicinal products (IMPs) for this study are astegolimab and placebo. Standard of care COPD maintenance therapies (as specified in Section 6.1.1), having been used prior to screening and continued throughout the study, are considered *Auxiliary Medicinal Products (AxMPs)*/non-investigational medicinal products (NIMPs). Appendix 11 *and Appendix 12* identify all investigational and *AxMPs*/NIMPs for this study.

6.1 STUDY TREATMENT ADMINISTERED

Table 5 provides a description of assigned study treatments for this study.

Table 5 Study Treatment Description

	Astegolimab	Placebo
Use	Experimental	Placebo comparator
Drug form	Liquid	Liquid
Unit dose strength(s)	[redacted]	Not applicable
Dosage level(s)	476 mg Q2W or Q4W	0 mg Q2W or Q4W
Formulation(s)	Refer to Investigator's Brochure	Not applicable
Packaging	[redacted]	[redacted]
Labeling	Per local requirements	
Route of administration	SC injection	SC injection
Source	Sponsor	Sponsor

Q2W = every 2 weeks; Q4W = every 4 weeks.

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

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) [redacted]

[redacted] See the pharmacy manual for details on study drug preparation and administration.

All participants 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 participant develops any signs or symptoms to suggest a systemic hypersensitivity reaction or anaphylactic event, longer observation may be warranted as per the opinion of the investigator.

There must be a minimum of 8 days between doses. In the event a dosing visit would occur within *less than* 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.

Participants 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 participant to resume study drug.

At applicable sites, study treatment may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in mobile nursing (MN) visits. The Sponsor will select a professional MN service for participating sites, or sites may have the option to use their own professional MN staff, where appropriate and approved by the Sponsor, wherein MN staff will be trained on ICH GCP, protocol-specific requirements, anaphylaxis management, handling of adverse events/serious adverse events, and how to contact the site staff.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 4.

6.1.1 Standard of Care COPD Maintenance Therapy

All participants must be on optimized, stable COPD maintenance therapy. This includes ICS therapy plus LABA, or LABA plus LAMA, or ICS plus LABA and LAMA for ≥ 12 months prior to Visit 1 and with stable doses of medications for at least 4 weeks prior to Visit 1.

There should be no anticipated changes in therapy prior to initiation of study drug and throughout the study (see Section 6.8.3 for more details).

Initiation of new COPD therapy, including a methylxanthine preparation, maintenance macrolide therapy, and/or a PDE4 inhibitor, is not permitted within 4 weeks prior to Visit 1.

Maintenance oral corticosteroid therapy at doses of $\leq$10 mg/day prednisolone or equivalent are permitted during screening and during study participation.

Maintenance oral corticosteroid therapy at doses $>$10 mg/day prednisolone or equivalent are not permitted within 4 weeks prior to Visit 1.

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

At screening, participants will be instructed on the proper technique recommended for administration of their inhaled COPD 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 participant may be switched to another brand or formulation that is equivalent to the medication that the participant was receiving at the time of study entry.
Proposed changes should be discussed with the Medical Monitor. All changes to a participant's background medications should be documented in the Concomitant Medications electronic Case Report Form (eCRF).

6.2 PREPARATION, HANDLING, STORAGE, 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 participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants 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 an interactive voice or web-based response system (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 participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

Investigational medicinal products 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 preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT AND BLINDING

6.3.1 Treatment Assignment

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

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

6.3.2 Blinding

Study site personnel and participants will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to participant treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

While PK and immunogenicity samples must be collected from participants assigned to the comparator arm to maintain the blinding of treatment assignment, PK and anti-drug antibody (ADA) assay results for such participants are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participant treatment assignments to identify appropriate samples for analysis. Pharmacokinetic samples from participants assigned to the comparator arm will not be analyzed for study drug PK

concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all participants. Postbaseline immunogenicity samples from participants assigned to the comparator arm will not be analyzed for ADAs except by request.

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

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

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

6.4 STUDY TREATMENT COMPLIANCE

The treatment regimens are summarized in Section 6.1.

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 participant’s home or another suitable location, if the participant has given written informed consent to participate in MN visits.

Details on study drug administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section A3–7.12.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 3.

6.5 DOSE MODIFICATION

Modification of the astegolimab dose is not permitted.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Participants may be eligible to receive astegolimab as part of an extension study, as described in Section 4.1.2. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities

6.8 CONCOMITANT THERAPY

Any COPD-specific medications, biologics, and other immunomodulatory therapy used by a participant in addition to protocol–mandated treatment from 12 months prior to initiation of study treatment to the end of study/safety follow-up visit must be recorded on the Concomitant Medications eCRF.

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

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 participant 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.

6.8.1 Rescue Therapy

It is expected that participants will be using short-acting anticholinergic and/or short-acting β-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 participant's prescribed inhaler or nebulizer.

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.

6.8.2 Systemic Corticosteroids

Participants 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 5.2).

Chronic maintenance treatment with oral, IV, or IM corticosteroids > 10 mg/day prednisolone equivalent is not permitted during the study treatment period.

The use of oral, IV, or IM corticosteroids is permitted for acute participant 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 6 for additional details on restrictions for use of systemic corticosteroids.

6.8.3 COPD Therapy and Concomitant Therapy Restrictions

Restrictions regarding the use of COPD therapy and concomitant therapy are summarized in Table 6.

Table 6 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 • LABA + LAMA • 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 6.1.1

Table 6 COPD Therapy and Concomitant Therapy Restrictions (cont.)

Therapy	Restrictions for Use	
	Prior to Study Treatment	During Study Treatment
Non-biologic immunomodulatory or immunosuppressive therapy (e.g., methotrexate, troleandomycin, 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 [b]
Astegolimab	Prohibited (any use) prior to study	—
Methylxanthine preparations [b], 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	Prohibited during study treatment [a]
Pulmonary rehabilitation	Participation in, or scheduled for, an intensive COPD rehabilitation program *is prohibited* (participants who are in the maintenance phase of a rehabilitation program are eligible)	Initiation of new pulmonary rehabilitation program prohibited during study treatment *is prohibited* [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; IL = interleukin; IM = intramuscular; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase 4; SOC = standard of care.

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

[b] Unless indicated for an acute COPD exacerbation (as defined in Section 8.3.1).

[c] Participants who are in the maintenance phase of a rehabilitation program are eligible (see Section 5.1).

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

6.8.4 Cautionary Therapy

6.8.4.1 Herbal Therapies

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

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. See the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant'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 participant
- Pregnancy
- Cases of potential drug-induced liver injury that includes elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.7)

Participants who discontinue study treatment prematurely should be asked to continue with all scheduled study assessments (see Section 8 for additional details).
Any participant that discontinues study treatment prematurely will not be eligible to participate in OLE Study GB43374 (see Section 4.1.2).

If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator. The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). See the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) 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.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 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 individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

8.2 MEDICAL HISTORY, BASELINE CONDITIONS, CONCOMITANT MEDICATION, AND DEMOGRAPHIC DATA

Medical history and baseline conditions, including clinically significant diseases, surgeries, reproductive status, smoking history and use of alcohol will be recorded at screening. Any COPD-specific medications, biologics, and other immunomodulatory drugs used by the participant from 12 months prior to the initiation of study treatment and over-the-counter or prescription medicines, vitamins, and/or herbal supplements used by the participant from 4 weeks prior to *screening* will be recorded. Demographic data, including age, sex, and self-reported race or ethnicity, will also 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 12 months prior to the initiation of study drug, and a participant-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.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be

administered only if the clinical assessment and local laboratory test values are acceptable.

At applicable sites, certain study assessments may be performed by a MN professional at the participant's home or another suitable location, to improve access and convenience for participants participating in the study. The Sponsor will select a healthcare company that will be responsible for providing professional MN services for participating sites (the MN vendor), or sites may have the option to use their own professional MN staff, where appropriate and approved by the Sponsor. MN staff will be trained on ICH GCP, protocol-specific requirements, anaphylaxis management, handling of adverse events/serious adverse events, and how to contact the site staff. The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Section 1.3) will specify the assessments that may be performed by an MN professional.

8.2.1 Smoking History

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

Participants may discontinue smoking at any time during the study.

8.2.2 Smoking Cessation for Current Smokers

At screening, participants who are current smokers (as defined in Section 5.1) will receive smoking cessation counseling.

> A current smoker is defined as a participant who has used inhaled tobacco products or inhaled marijuana within 6 months prior to screening, through use of cigarettes, cigars, electronic cigarettes, vaporizing devices, or pipe.

Participants 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. Participants may be referred to their primary care physician or local services, as applicable, for further smoking cessation support.

8.2.3 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.

8.3 EFFICACY ASSESSMENTS

8.3.1 COPD Exacerbation Assessment

At each study visit, an assessment will be conducted to determine if the participant experienced any protocol-defined acute COPD exacerbations since the previous study visit.

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 Appendix 3. Sites should record all medications used for treatment of any COPD exacerbation in the appropriate eCRF.

8.3.2 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, participant 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 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 according to the schedule of assessments in Table 1. For safety reasons, consideration should be given to omitting spirometry if a participant is having an acute COPD exacerbation event (as defined in Section 8.3.1) at the time of the scheduled study visit.

8.3.2.1 Pre-Bronchodilator Spirometry

Pre-bronchodilator spirometry evaluations must be performed before use of bronchodilators. Chronic obstructive pulmonary disease therapies that may affect spirometry must be withheld until pre-bronchodilator spirometry measurements are completed. Participants 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:

- LABA twice a day (BID) and LAMA BID: prohibited within 12 hours prior to spirometry
- LABA once a day (QD) and LAMA QD: 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 participant 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 Table 1.

8.3.2.2 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 4 inhalations. The FEV_1 measurements should be recorded 20–30 minutes after bronchodilator use. For visits that require pre-bronchodilator spirometry, bronchodilator administration should be administered between 15–45 minutes after pre-bronchodilator spirometry.

8.3.3 Clinical Outcome Assessments

The clinical outcome instruments (i.e., PROs) will be completed to assess the treatment benefit and participant experience of astegolimab.

The PRO data will be collected through use of the following instruments: Saint George's Respiratory Questionnaire (SGRQ-C), modified Medical Research Council Dyspnea scale (mMRC), an eDiary that includes EXAcerbations of Chronic Pulmonary Disease Tool (EXACT) and the Evaluating Respiratory Symptoms in COPD (E-RS:COPD), and the EuroQoL 5-Dimension Questionnaire (EQ-5D-5L).

8.3.3.1 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 participant'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 7.

8.3.3.2 Modified Medical Research Council Dyspnea Scale

The mMRC assesses activity-associated dyspnea via a single item that requires participants to select 1 of 5 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 participant's current status at the timepoint of administration. A copy of the scale is provided in Appendix 7.

8.3.3.3 EXACT Questionnaire and E-RS:COPD Subset

The EXACT is administered as an eDiary that assesses COPD exacerbations (Leidy et al. 2010). The 14-item questionnaire contains 4 domains: breathlessness (5 items), cough and sputum (3 items), chest symptoms (3 items), and additional attributes (tired or weak, sleep disturbance, and scared or worried – 3 items). The EXACT has a recall period of "today." The subset E-RS:COPD is composed of the breathlessness, cough and sputum, and chest symptoms domains of the EXACT (11 total items) and, as such, it specifically assesses COPD symptoms (Leidy et al. 2014). An E-RS:COPD total score is derived based on the 3 domains. The eDiary entry takes approximately 5 minutes to complete.

Participants are trained on the eDiary at screening. Participants are asked to complete the diary every evening before going to bed for 7 days prior to timepoints as specified in the schedule of assessments. A copy of the EXACT assessment is provided in Appendix 7. Note that while the EXACT will be administered in its entirely, per developer's instructions, only the E-RS will be used to support symptom endpoints in this study.

8.3.3.4 EuroQoL 5-Dimension Questionnaire

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman- et al. 2011; Janssen et al. 2013) (see Appendix 7). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale (VAS) that measures health state. The EQ-5D-5L is designed to capture a participant's current health status.

Published weighting systems allow for creation of a single composite score of the participant's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

8.4 SAFETY ASSESSMENTS

8.4.1 Physical Examinations

A complete physical examination, performed at screening and other visits, should include, at a minimum, 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 participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Limited physical examinations may be performed by an MN professional.

8.4.2 Vital Signs

Temperature, pulse rate, respiratory rate, peripheral oxygen saturation, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed while the participant is in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Vital sign measurement may be performed by an MN professional.

8.4.3 Electrocardiograms

Single ECG recordings will be obtained as outlined in the schedule of activities (see Section 1.3) and may be obtained at unscheduled timepoints as clinically indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine. ECG equipment, including software, will be dispensed to all sites. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the participant has been resting in a supine position

for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., *spirometry*, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), 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 reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Clinically significant waveform changes or other clinically significant ECG abnormalities must be documented by the investigator as adverse events on the Adverse Event eCRF.

Digital recordings will be stored at the central ECG laboratory and the ECG parameter data (e.g., QTc) will be sent to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean 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 at the investigator's discretion. If a PK sample is not scheduled for that timepoint, an PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Appendix 4. The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

8.4.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 weeks of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are

considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by an MN professional.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.4.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.5 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.5.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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 (see Appendix 3). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 12 weeks after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3)*, or until the last study visit, whichever is later. If a participant enrolls into the Open Label Extension (OLE) study GB43374, then any adverse events occurring prior to the first dose of open-label astegolimab should be recorded in GB44332.*

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.5.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.5.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.5.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs or ECs, and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious 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.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Astegolimab Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.5.5 Pregnancy

Female participants 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 astegolimab.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 12 weeks after the final dose of astegolimab.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

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 Appendix 5. The Sponsor or a designee may follow up by telephone, fax, e-mail, 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.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.5.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.5.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.5.8 Adverse Events of Special Interest

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 the investigator becomes aware of the event; see Section A3–5 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 A3–7.7)
- Suspected transmission of an infectious agent by a study treatment, 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- MACE, defined as 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. *Only systemic reactions as described in Section A4–1.2.2 are required to be reported by the investigator to the Sponsor immediately.*

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 4.

8.5.9 Medical Device Complaints

In this study, the astegolimab/placebo prefilled syringe with needle safety device (PFS-NSD) and physical activity monitor are considered medical devices. The investigator must report all medical device complaints and any associated adverse events to the Sponsor, as described in Appendix 6.

8.5.10 Medical Monitors and 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.

Contact Information for PPD

Emergency Medical Contact:	PPD Pharmacovigilance Group Europe, Middle East, Africa, Asia Pacific Region
Safety Hotline Telephone No.:	+44 1223 374 240
Safety Hotline Fax No.:	+44 1223 374 102
Emergency Medical Contact:	PPD Pharmacovigilance Group North America
Safety Hotline Telephone No.:	+1 (888) 483-7729
Safety Hotline Fax No.:	+1 (888) 529-3580
Emergency Medical Contact:	PPD Pharmacovigilance Group Latin America
Safety Hotline Telephone No.:	+55 11 4504 4801
Safety Hotline Fax No.:	+55 11 3958 0983

To ensure the safety of study participants, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.6 PHARMACOKINETICS

Serum PK samples will be collected for measurement of serum concentrations of astegolimab as specified in the schedule of activities (see Section 1.3). Serum PK samples will be sent to the Sponsor or designee for analysis.

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of PK samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of astegolimab.
Samples collected for analyses of astegolimab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.11.2), PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

Information on unblinding of personnel responsible for performing PK assays is provided in Section 6.3.2.

8.7 PHARMACODYNAMICS

See Section 8.9 for information on PD biomarkers.

8.8 GENETICS

See Section 8.9 and Appendix 10 for information on genetic biomarkers.

8.9 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood, plasma and serum samples for exploratory research on biomarkers, including biomarker assay development

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., C-reactive protein), and DNA single nucleotide polymorphisms (SNPs) of selected genes (e.g., *IL1R1*, *IL33*, and other genes related to COPD). Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, SNPs and other genomic variants; and genomic profiling. Genomic research may include exploration of germline variants. Genomic profiling will not include whole genome sequencing (WGS) or whole exome sequencing (WES).

Residual serum PK or immunogenicity samples may be used for exploratory biomarker research described above.

Biomarker samples will be collected according to the schedule outlined in Section 1.3. Sample collection may be performed by an MN professional. Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.11.2), biomarker samples will be destroyed no later than 10 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-

approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants 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.

8.10 IMMUNOGENICITY ASSESSMENTS

Serum samples will be collected for evaluation of antibodies to astegolimab as specified in the schedule of activities. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee. Instructions for the collection and handling of serum immunogenicity samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Serum samples will be screened for antibodies binding to astegolimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to astegolimab and/or further characterize the immunogenicity of astegolimab.

The detection and characterization of antibodies to astegolimab will be performed through use of a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for astegolimab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.9 and 8.11.2 if applicable), immunogenicity samples will be destroyed no later than 5 years (or according to local regulations) after the final Clinical Study Report has been completed to enable further analysis of immune responses to astegolimab or immunogenicity assay development and validation (if needed).

8.11 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.11.1 Optional Physical Activity Monitoring (Participants Providing Separate Consent)

Approximately 150 consenting participants at participating sites will wear a physical activity monitor to assess changes in participant 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, participant motivation, and functional capacity. The monitor will be worn for 4 periods of up to 2 weeks each

(minimum of 1 week) during the study. Participants 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 participants, 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. The investigator should document whether or not the participant has given consent to participate and (if applicable) the date of consent, by completing the appropriate eCRF.

8.11.2 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.11.2.1 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 participants who give specific consent to participate in this optional research. The 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

8.11.2.2 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 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 8.11.2) will not be applicable at that site.

8.11.2.3 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 sample for RBR collected at V2.
- Leftover blood, plasma, and serum 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 WGS, 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.

Research Biosample Repository 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).

8.11.2.4 Data Protection, Use, and Sharing

Research Biosample Repository samples and associated data will be labeled with a unique participant identification number.

Participant 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 participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, 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 participants, unless required by

law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following e-mail address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

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.

8.11.2.5 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 participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples 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 participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date 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.

8.11.2.6 Withdrawal from the Research Biosample Repository

Participants 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. 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 participant 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 participant'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 participant 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 participant number to the following email address:

global.rcr-withdrawal@roche.com

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

8.11.2.7 Monitoring and Oversight

Research Biosample Repository 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 an individual's 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.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary estimand of interest for this study is the rate ratio (RR) for annualized COPD exacerbation rate ratio.

For each of the two treatment groups (astegolimab Q2W or Q4W), the null hypothesis (H_0) for the primary endpoint is that the annualized exacerbation rates (AER) are the same in treatment and placebo arm. The alternative hypothesis (H_1) is that the AERs are different between the treatment and placebo arm:

$$H_0: RR = 1 \text{ versus } H_1: RR \neq 1$$

The null and alternative hypothesis will be tested at a two-sided 0.05 significance level for each of the two treatment groups compared with placebo. Null and alternative hypotheses of a similar form will be tested for all key secondary efficacy analyses. All hypothesis tests will be two-sided unless stated otherwise.

9.1.1 Sample Size Determination

During the global enrollment phase, a total of approximately 1290 participants will be randomly allocated in a 1:1:1 ratio to receive astegolimab Q2W, astegolimab Q4W, or placebo. The sample size provides approximately 90% power to detect a 20% reduction in annualized COPD exacerbation rate (0.8 RR) between one astegolimab arm and the placebo arm, assuming a 1.5 AER in the placebo arm, a 15% dropout rate, a two-sided significance level of 0.05, and a Poisson overdispersion parameter of 1.3.

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

1. Astegolimab Q2W compared with placebo

2. Astegolimab Q4W compared with placebo

For the *annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period in patients with low baseline blood eosinophil level (<300 cells/µL) and* secondary efficacy endpoints, hypothesis testing will be gated on the success of the primary efficacy endpoint. For each astegolimab dose arm tested to be statistically different from placebo in the primary endpoint, *these* endpoints will be tested within the dose arm. The list of efficacy endpoints to be included in the testing hierarchy and their testing orders will be specified in the SAP.

After completion of the global enrollment phase, additional participants may be enrolled at China's sites in an extended China enrollment phase, and at Japan's sites in an extended Japan enrollment phase.

9.2 ANALYSIS SETS

The analysis data sets for the purposes of analysis are presented in Table 7.

Table 7 Analysis Data Sets

Analysis Data Sets	Description
ITT	• All randomized participants, whether or not the participant received the assigned treatment • Participants will be grouped according to the treatment assigned at randomization by the IxRS
mITT	• All randomized participants who received at least 1 dose of study drug • Participants will be grouped according to the treatment assigned at randomization by the IxRS
Safety evaluable	• All randomized participants who received at least 1 dose of study drug • Participants will be analyzed based on the treatment they actually received (which may be different from the treatment to which the participant was randomized)
Pharmacokinetic evaluable	• *All randomized participants who received at least 1 dose of study drug and had at least one postdose PK assessment*
Immunogenicity evaluable	• *All randomized participants with at least one postdose ADA assessment*

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

9.3 STATISTICAL ANALYSES

The Statistical Analysis Plan (SAP) will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.3.1 General Considerations

Efficacy analyses will be conducted on the modified intent-to-treat (mITT) population (see Table 7).

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

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

The primary efficacy analysis will be performed when all patients globally, excluding the China and Japan extension cohorts, have completed or discontinued from the 52-week double blind treatment period.

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

9.3.2 Primary Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo in the mITT population 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 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.

9.3.2.1 Primary Estimand

The primary estimand is defined as follows:

- Population: *Individuals* with COPD who are former or current smokers and have a history of frequent exacerbations
- Variable: annualized rate of moderate and severe COPD exacerbations over the 52-week treatment period
- Treatments:
  - Experimental: astegolimab Q2W
  - Experimental: astegolimab Q4W
  - Control: placebo
- Intercurrent events *and handling strategies*:
  - *Use of prohibited medications for management of COPD exacerbation risk that leads treatment discontinuation: the event will be classified as a "moderate COPD exacerbation" under the composite strategy. Additionally, since participants may continue in the study after treatment discontinuation, all subsequent measurements after the prohibited medication use will be censored (hypothetical strategy). Such prohibited medications include any new prescriptions occurring after seven days of randomization of the following: theophylline, azithromycin, erythromycin, roflumilast, omalizumab, dupilumab, mepolizumab, reslizumab, benralizumab, tezepelumab, tozorakimab, itepekimab, prednisolone equivalent of >10 mg/day (systemic: oral, IV or IM) and pulmonary rehabilitation.*
  - *Treatment discontinuation not due to the use of prohibited medications for management of COPD exacerbation risk: the treatment effect of interest is irrespective of treatment discontinuation. Therefore, all data collected after the treatment discontinuation will be included in the analysis (i.e., treatment policy strategy).*

- *Change to initial treatment regimen: the treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug, changes to SOC, and the use of prohibited medication other than the ones for management of COPD exacerbation risk and leading to treatment discontinuation. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis (i.e., treatment policy strategy).*
- *Death not related to COPD exacerbation: data will be censored after the death occurrence (i.e., hypothetical strategy).*

- Summary measure: rate ratio (RR) for annualized rate of moderate and severe COPD exacerbations

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

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

9.3.2.2 Main Analytical Approach for Primary Endpoint

The AER will be estimated as the total number of COPD exacerbations observed over the treatment period divided by the total participant-years at risk. For each individual participant, years at risk will be derived as the number of days from the date of randomization to the date of completion or discontinuation of study in the double-blind treatment period, divided by 365.25 days. The adjusted AER will be estimated using a Negative Binomial regression model. The regression model will be adjusted for baseline covariates, as described in Section 9.3.1. In addition, *the natural log transformation of the* participant'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.

9.3.2.3 Sensitivity Analyses for Primary Endpoint

Sensitivity analysis using Poisson regression model and/or using baseline FEV_1 as an additional adjustment variable

The primary efficacy endpoint will be analyzed using a Poisson regression model as a sensitivity analysis. The same model (i.e., one adjusted for the same covariates as described in Section 9.3.2.2) will be used. A different model additionally adjusted for baseline FEV_1 (i.e., one adjusted for baseline FEV_1 and the covariates described in Section 9.3.1), will also be used for both the Negative Binomial and Poisson regression

model. All other elements of the analysis will remain the same as in the primary analysis.

Sensitivity analysis using composite strategy for death not related to COPD exacerbation

In the main analysis specified in Section 9.3.2.2, intercurrent event of death not related to COPD exacerbation will be treated with a hypothetical strategy. A sensitivity analysis using a composite strategy will be performed where the death not related to COPD exacerbation will be considered as a "severe COPD exacerbation". All other elements of the analysis will remain the same as in the primary analysis.

Sensitivity analysis using region stratification factor from IxRS

In the main analysis specified in Section 9.3.2.2, for model adjustment, region will be allocated based on the country a study site is located in. A sensitivity analysis will be performed using region as per the manual data entry in IxRS by the study sites. All other elements of the analysis will remain the same as in the primary analysis.

Tipping point analysis

For the primary endpoint, tipping point analysis via multiple imputation of event counts assuming a range of deltas will be performed. Event counts will be imputed at the participant level for the observed period between the last study visit and Week 52 visit for participants who discontinued from the study early. A range of delta values will be used to adjust the underlying event rate used for imputation in the astegolimab and placebo arms independently based on a grid of delta adjustment. The range of delta values will include cases where dropouts from the astegolimab arm are assumed to have worse outcomes than dropouts from the placebo arm. The goal is to identify the tipping point which is the minimum shift that is needed to make the result non-significant.

Additional supplementary analyses, including subgroup analyses, may be performed, and details will be pre-specified in the SAP.

9.3.2.4 *Secondary Estimand*

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

9.3.3 Estimation Methods for the Secondary Endpoints

9.3.3.1 Secondary Endpoints

The secondary efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo in the mITT population 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 HRQoL at Week 52, as assessed through the SGRQ-C total score
- Absolute change from baseline in post-bronchodilator FEV_1 (liters) at Week 52
- Absolute change from baseline in E-RS:COPD total score at Week 52
- Proportion of participants with improvement in HRQoL, defined as a decrease from baseline of ≥ 4 points in SGRQ-C total score, at Week 52
- Annualized rate of severe COPD exacerbations over the 52-week treatment period

The secondary endpoints will be analyzed in the mITT population. Time-to-event endpoints will be analyzed using log-rank test and Cox proportional hazards regression models. Continuous endpoints will be summarized by treatment arm and timepoints, and analyzed using mixed models for repeated measures. Improvement in HRQoL will be summarized as proportion of responders, i.e., patients achieving pre-specified improvement, and analyzed using logistic regression models. Full details of analysis methods, data handling, sensitivity analyses, and type I error control will be described in the SAP.

9.3.3.2 Safety Analyses

The safety analysis population will consist of all randomized participants who received at least 1 dose of study drug (full or partial dose), with participants grouped according to treatment received.

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

Study treatment exposure (such as total number of doses received) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to the Division of AIDS Table v2.1 (see Appendix 8). A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest (Section 8.5.8), adverse events leading to discontinuation from study treatment, and adverse events leading to discontinuation from study will be summarized by mapped terms, appropriate thesaurus level, and severity

grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized. Summary measures include counts and percentages of participants with the adverse event under analysis.

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

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

Details regarding safety analyses will be described in the SAP.

9.3.4 Exploratory Analyses

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

9.3.4.1 Summaries of Conduct of Study

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

9.3.4.2 Summaries of Demographics and Baseline Characteristics

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

9.3.4.3 Pharmacokinetic Analyses

Individual and mean *serum* matrix astegolimab concentration versus time data will be tabulated and plotted by dose level. The PK data from this study may be used in the population PK analysis. 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 drug-elimination half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, and range). Inter-participant variability and drug accumulation will be evaluated.

Additional PK analyses will be conducted as appropriate.

9.3.4.4 Immunogenicity Analyses

The immunogenicity analysis population will consist of all participants with at least one postdose ADA assessment. Participants will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

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

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

9.3.4.5 Biomarker Analyses

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

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

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

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

9.3.4.6 China Subpopulation Analyses

The global population will include all participants enrolled during the global enrollment phase (including participants enrolled at China's sites during that phase), and the China

subpopulation will include all participants enrolled at China's sites (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subpopulation, and results from the China subpopulation analyses will be summarized in a separate Clinical Study Report.

9.3.4.7 *Japan Subpopulation Analyses*

The global population will include all participants enrolled during the global enrollment phase (including participants enrolled at Japan's sites during that phase), and the Japan subpopulation will include all participants enrolled at Japan's sites (i.e., during both the global enrollment phase and the extended Japan enrollment phase). Separate analyses will be performed for the global population and the Japan subpopulation, and results from the Japan subpopulation analyses will be summarized in a separate Clinical Study Report.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) or Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 Code of Federal Regulations (CFR, U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trial Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 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 study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant’s legally authorized representative.

A1–4 DATA PROTECTION

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.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 300 sites globally will participate to enroll approximately 1290 participants *in the global enrollment phase. After completion of the global enrollment phase, additional participants may be enrolled at China's sites in an extended China enrollment phase, and at Japan's sites in an extended Japan enrollment phase.* Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2.

An independent Data Monitoring Committee will be employed to monitor and evaluate participant safety throughout the study.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and 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, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, and will be provided 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/

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

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the Case Report Form.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the Case Report Form by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the Case Report Form or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results.
In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site 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.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant 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.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the central laboratory, except where specified.

Local laboratory results are only required in the event that the central laboratory results are not available in time for study treatment administration and/or response evaluation. If a local sample is required, it is important that a sample for central analysis be obtained at the same time *(except if the reason for using local labs is that the central lab is not available or sample shipment to the central lab is interrupted)*. Additionally, if the local laboratory results are used to make either a study treatment decision or a response evaluation, the results must be entered on the electronic Case Report Form.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Laboratory Tests
• Chemistry panel (serum or plasma): bicarbonate, sodium, potassium, chloride, glucose, urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, and AST • Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) • Pregnancy test All female participants of childbearing potential will have a serum pregnancy test performed at screening. Urine pregnancy tests will be performed locally at subsequent visits prior to study drug administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Investigators must document their review of each laboratory safety report.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- *Medically significant*:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 A3–3.2); 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 electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will use the DAIDS toxicity grading scale (Health and Human Services 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 A3-1 for assessing the severity of adverse events that are not specifically listed in the DAIDS toxicity grading scale.

Table A3-1 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 DAIDS, 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.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of

causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

New or updated information should be recorded on the originally completed Adverse Event eCRF. 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 the investigator becomes 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

During the adverse event reporting period (defined in Section 8.5.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, 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.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 12 weeks after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail 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 more than 12 weeks after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING 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 (*see Section 8.5.1*), if the event is believed to be related to prior exposure to study treatment. 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 e-mailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or e-mail address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF.

Avoid colloquialisms and abbreviations. Only 1 adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 INJECTION SITE REACTIONS

Adverse events that occur during or within 24 hours of study drug administration and are considered to be related to study drug injection should be captured as a diagnosis (e.g., “injection-related reaction”/“injection site 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 Injection Reaction eCRF. If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate event on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

A3–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

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.

A3–7.3 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 3 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.

A3–7.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant 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 the investigator becomes aware that the event became serious; see Section A3–5 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 participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease 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., dose 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 × upper limit of normal (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 A3–7.4 for details on recording persistent adverse events).

A3–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease 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., dose 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 A3–7.4 for details on recording persistent adverse events).

A3–7.7 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 A3–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.8 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.5.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). 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 1 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 A3–6.

A3–7.9 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").

A3–7.10 LACK OF EFFICACY OR WORSENING OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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 8.3.1).

A3–7.11 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 A3–2), 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 participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant 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 participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.12 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 and adverse events associated with special situations are to be reported separately on the Adverse Event eCRF, as outlined in the sections below.

A3–7.12.1 Reporting Special Situations

All special situations associated with astegolimab or matching 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, 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.

A3–7.12.2 Reporting Adverse Events Associated with Special Situations

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 the investigator becomes aware of the event; see Section A3–5). For astegolimab or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- 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.

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose (special situation) and 1 entry to report the adverse event (headache).
The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

A3–7.13 PARTICIPANT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

A3–7.14 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 participant management.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

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Astegolimab is not approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with astegolimab in 7 completed Phase I and Phase II studies and 1 ongoing Phase II study, in healthy volunteers and participants with asthma, atopic dermatitis, chronic obstructive pulmonary disease (COPD), and coronavirus disease 2019 (COVID-19) pneumonia (see Section 2.3.2). As of the data cutoff of 10 February 2023 a total of approximately 583 patients and 109 healthy subjects have been exposed to at least 1 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 participants participating in this study. Eligibility criteria have been designed to exclude participants at higher risk for toxicities. Participants 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.

A4–1 RISKS ASSOCIATED WITH ASTEGOLIMAB

A4–1.1 IDENTIFIED RISKS

No risks have yet been identified for astegolimab.

A4–1.2 POTENTIAL RISKS

A4–1.2.1 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 anti-drug antibody (ADA) development in ongoing studies, serum samples will be collected from participants at protocol-defined intervals. Participants 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.

A4–1.2.2 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, 1 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.

Participants 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.

A4–1.2.3 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%–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.

A4–1.2.4 Infection

The intended mechanism of action of astegolimab suggests inhibitory effects on immune responses mediated by T helper 2 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 interleukin [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 3 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.

A4–1.2.5 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 3 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 glycosylated hemoglobin 1c (HbA_{1c}), fasting glucose, and lipids. In the completed Phase II studies, none of the potential major adverse cardiovascular events (MACE) were considered related to study drug or led to discontinuation of treatment, and all events were resolved.

Participants with active or unstable recent cardiovascular disease are excluded from the study. 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.

A4–2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A4–2.1 TREATMENT INTERRUPTION

Study treatment may be temporarily suspended in participants who experience treatment-emergent adverse events considered to be related to study drug. If study drug has been withheld for more than 2 consecutive scheduled doses because of an ongoing adverse event, the participant 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.

A4–2.2 MANAGEMENT GUIDELINES

Guidelines for management of specific adverse events are outlined in Table A4-1. Additional guidelines are provided in the subsections below.

Table A4-1 Guidelines for Management of Participants Who Experience Adverse Events

Event	Action to Be Taken
Hepatic Event	
ALT or AST increase that meets Hy's Law criteria (see Section A3–7.7): 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. • Report event as an AESI (see Section 8.5.8).
If abnormal liver function values, but the criteria for Hy's Law are not met: ALT or AST increase that meets at least 1 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 abnormal laboratory values or clinical 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 8.5.8).

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

[a] See Section 8.5.8 for examples of events that qualify as major adverse cardiovascular events.

A4–2.2.1 Management of Increases in QT Interval

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

- Sustained (at least 2 ECG measurements > 30 minutes apart) QT interval corrected with use of Fridericia's formula (QTcF) that is > 500 ms and > 60 ms longer than the baseline value
- Sustained absolute QTcF that is > 515 ms (or > 530 ms for participants 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 participants with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until 2 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 participants.

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

A4–2.2.2 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.

Appendix 5
Collection of Pregnancy Information

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A5–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants 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 astegolimab. 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 the investigator becomes aware of the pregnancy), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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 or 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.

A5–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 12 weeks after the final dose of astegolimab. 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 e-mailing the form using the fax number or e-mail 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 participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for 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 participant 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.

A5–3 ABORTIONS

A spontaneous abortion in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment 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 the investigator becomes aware of the event; see Section A3–5).

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 the investigator becomes aware of the event; see Section A3–5). 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.

A5–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment 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 the investigator becomes aware of the event; see Section A3–5).

Appendix 6
Reporting Requirements for Medical *Product* Complaints

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A6–1 REPORTING REQUIREMENTS FOR MEDICAL *PRODUCT* COMPLAINTS

A medical product complaint is report that expresses dissatisfaction with a product's identity, quality, safety, strength, purity, reliability, durability, usability, performance, or effectiveness. The investigator must report all *product complaints related to the astegolimab pre-filled syringe with a needle safety device*. The investigator should *provide all necessary documentation,* including the product batch number, *to the Clinical Research Associate (CRA), who will start the Sponsor's internal complaints process*. If the *product complaint* results in an adverse event to the study participant, the event must be reported on the Adverse Event electronic Case Report Form (eCRF) and submitted through the electronic data system. If the event fulfills seriousness criteria, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as outlined in Section A3–5.

Appendix 7
Clinical Outcome Assessment Instruments

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A7–1 CLINICAL OUTCOME ASSESSMENT INSTRUMENTS

The clinical outcome instruments (i.e., PROs) will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3) and the EXAcerbations of Chronic Pulmonary Disease Tool (EXACT) will be self-administered at home on a daily basis for at least 7 days prior to specified timepoints. At the clinic, instruments will be administered before the participant 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.

Participant-reported outcome instruments will be translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor.

The Saint George's Respiratory Questionnaire–COPD (SGRQ-C), EuroQol 5-Dimension (EQ-5D-5L), and modified Medical Research Council Dyspnea Scale (mMRC) will be completed via tablet device used at the clinic and the EXACT via take-home electronic Diary (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 and instructions for completing the instruments electronically will be provided by the site staff. 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 participants will receive hands-on training in use of the eDiary, including review of the User Guide. Participants 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 days prior to Visit 2, must be demonstrated. Participants unable to demonstrate compliance with the eDiary will be screen failed. The participant will have the opportunity to demonstrate eDiary compliance if re-screened (see Section 8.1).

After randomization, eDiary compliance, defined as completion of all questions on at least 4 of 7 days each week (i.e., weeks specified for completion per Table 1), is required to optimize data quality and minimize the underestimation of symptom-defined events due to missing data.

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

- Participants should complete the instruments in a quiet area with minimal distractions and disruptions
- Participants should answer questions to the best of their ability; there are no right or wrong answers
- Participants 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:

- Participants' 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 participants 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
- Participants 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
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments

A7–2 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE–COPD

Do not reproduce or distribute. 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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St. George's Respiratory Questionnaire–COPD
PART 1 (cont.)

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

SGRQ-C (enUS) 15DEC2017 FINAL

St. George's Respiratory Questionnaire–COPD
PART 1 (cont.)

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…… ☐

SGRQ-C (enUS) 15DEC2017 FINAL

St. George's Respiratory Questionnaire–COPD
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

SGRQ-C (enUS) 15DEC2017 FINAL

St. George's Respiratory Questionnaire–COPD
PART 2 (cont.)

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

SGRQ-C (enUS) 15DEC2017 FINAL

St. George's Respiratory Questionnaire–COPD
PART 2 (cont.)

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

SGRQ-C (enUS) 15DEC2017 FINAL

St. George's Respiratory Questionnaire–COPD
PART 2 (cont.)

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.

SGRQ-C (enUS) 15DEC2017 FINAL

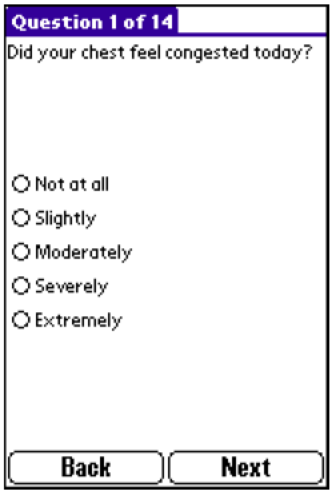
A7–3 ELECTRONIC DIARY (eDIARY)

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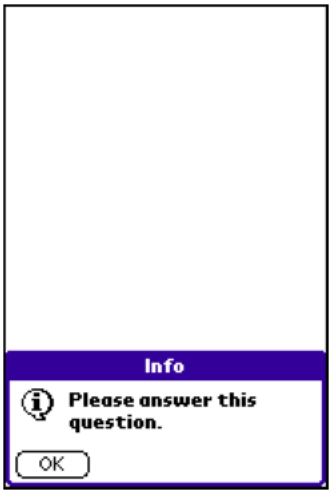
EXAcerbations of Chronic Pulmonary Disease Tool (EXACT®)



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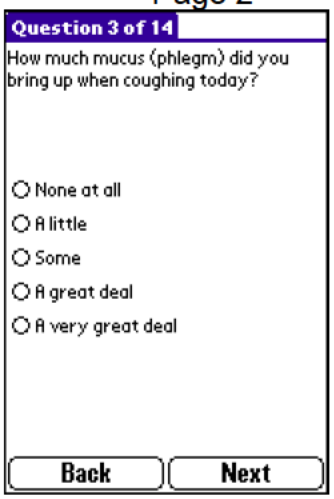


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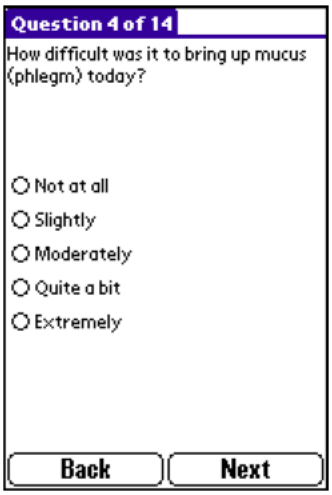




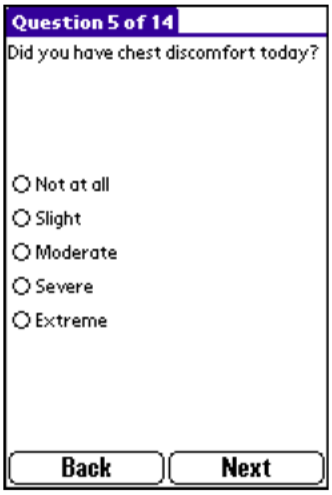
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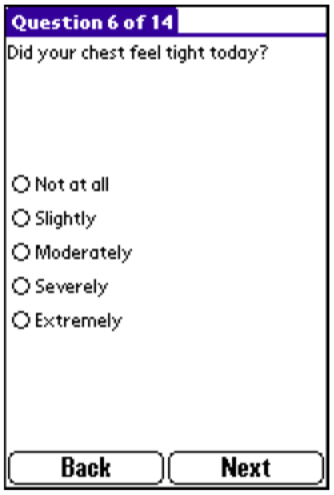
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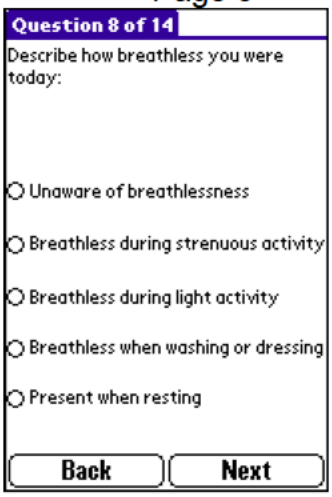
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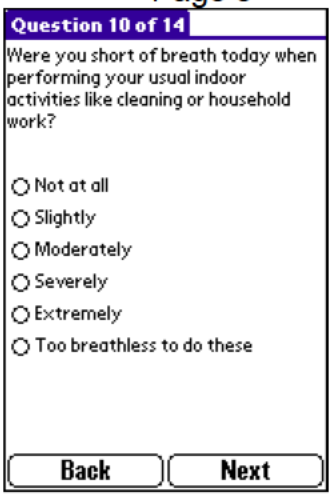
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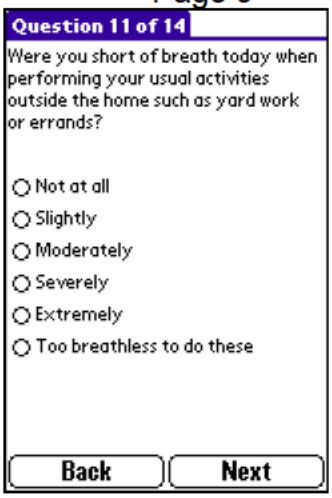
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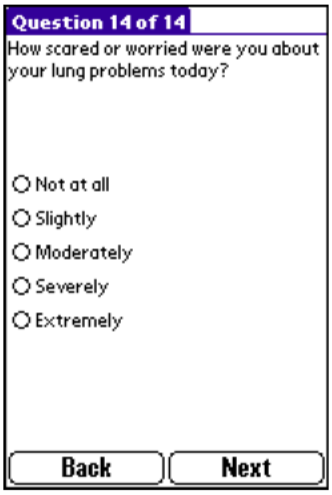
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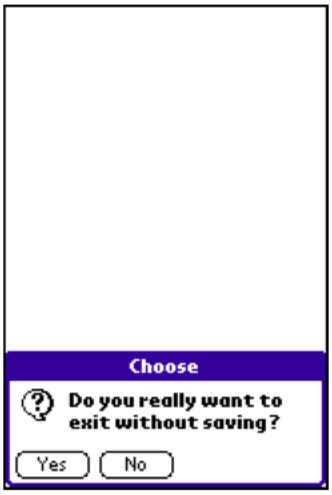
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A7–4 MODIFIED MEDICAL RESEARCH COUNCIL DYSPNEA SCALE

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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."

A7–5 EUROQOL EQ-5D-5L

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Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking	❑
I have slight problems walking	❑
I have moderate problems walking	❑
I have severe problems walking	❑
I am unable to walk	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

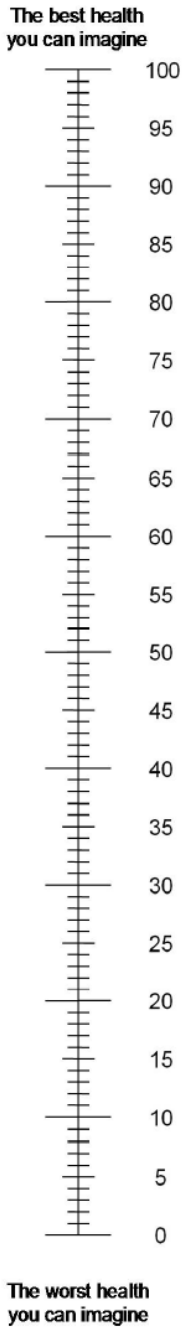
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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 (Health and Human Services 2017), with slight modifications for clarity and for alignment with internal practices, for assessing the severity of each adverse event reported during the study. In addition to the grading outlined in the following tables, all deaths related to an adverse event are to be classified as Grade 5.

Table A8-1 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
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

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.)				
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 ≤2 units packed RBCs (for children, packed RBCs ≤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 ≥0.25 seconds or Type I second-degree AV block	Type II second-degree AV block or ventricular pause ≥3.0 seconds	Complete AV block
Prolonged PR interval or AV block: ≤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 ≥3.0 seconds	Complete AV block

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)

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.)				
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	—	—
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

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				
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)
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)

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.)				
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	—
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

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.)				
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)
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

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.)				
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)
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	—	—

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.)				
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
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

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.)				
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
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

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.)				
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
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

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.)				
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
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)

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)
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	—
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	—

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				
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
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

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)
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)

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)

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.)				
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
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	—

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.)				
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)
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	≥38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to <40.0°C or ≥102.7 to <104.0°F	≥40.0°C or ≥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

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.)				
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)
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

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)

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

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 A8-2			
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)

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
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)

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, 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)	—
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)

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.)				
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	≥ 120 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)

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
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)

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.)				
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)
INR, high (not on anticoagulation therapy)	1.1 to < 1.5 × ULN	1.5 to < 2.0 × ULN	2.0 to < 3.0 × ULN	≥ 3.0 × ULN
Methemoglobin (% hemoglobin)	5.0% to < 10.0%	10.0% to < 15.0%	15.0% to < 20.0%	≥ 20.0%
PTT, high (not on anticoagulation therapy)	1.1 to < 1.66 × ULN	1.66 to < 2.33 × ULN	2.33 to < 3.00 × ULN	≥ 3.00 × ULN

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.)				
Platelets, decreased	100,000 to $<$125,000 cells/mm^3 (100.000×10^9 to $<125.000 \times 10^9$ cells/L)	50,000 to $<$100,000 cells/mm^3 (50.000×10^9 to $<100.000 \times 10^9$ cells/L)	25,000 to $<$50,000 cells/mm^3 (25.000×10^9 to $<50.000 \times 10^9$ cells/L)	$<$25,000 cells/mm^3 ($<25.000 \times 10^9$ 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 \times 10^9$ cells/L)
WBC, decreased: $\leq$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 \times 10^9$ cells/L)
Urinalysis				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or $\leq$250 mg	2+ or $>$250 to $\leq$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	$\geq$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	—

AV = atrioventricular; BMD = bone mass density; BMI = body mass index; BPAP = bi-level positive airway pressure; CD4 = cluster of differentiation 4; CPAP = continuous positive airway pressure; eGFR = estimated glomerular filtration rate; IV = intravenous; LLN = lower limit of normal; ULN = upper limit of normal; WHO = World Health Organization.

[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.

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

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

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

[f] See Section A3–7.1 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.

[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.

[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.

[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).

Table A8-2 Severity Grading for Events Not Specifically Listed in Table A8-1

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
5	*Fatal*

Appendix 9
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

Required Equipment and Medication

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), SC, IV, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.
7. Collect serum samples for immunogenicity testing.

Ask the participant to return for immunogenicity sample collection at the time of washout, if appropriate

Appendix 10
Genetics: Use and Analysis of DNA for Mandatory Samples

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to astegolimab and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to astegolimab and treatments of this drug class /or treatments of this drug class and chronic obstructive pulmonary disease (COPD). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

DNA samples will be analyzed for potential predictive biomarkers of astegolimab response in primary and secondary endpoints (e.g., exacerbation rate, time to first exacerbation and forced expiratory volume in 1 second) to assess if a subset of participants derives enhanced clinical benefit from astegolimab. Predictive biomarkers include, but are not limited to, germline variants in interleukin-1 receptor-like 1. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to astegolimab or study treatments of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on astegolimab and treatments of this drug class/or treatments of this drug class or COPD continues but no longer than 10 years or other period as per local requirements.

Appendix 11
Investigational Medicinal Product 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)*	*Unauthorized*	*Not applicable*
Astegolimab (RO7187807) placebo	*IMP (placebo)*	*Unauthorized*	*Not applicable*
LABA [a]	*AxMP (standard of care)*	*Authorized*	*Yes*
SABA [a]	*AxMP (standard of care)*	*Authorized*	*Yes*
LAMA [a]	*AxMP (standard of care)*	*Authorized*	*Yes*
SAMA [a]	*AxMP (standard of care)*	*Authorized*	*Yes*
ICS [a]	*AxMP (standard of care)*	*Authorized*	*Yes*
CS (oral, IV, IM) [a]	*AxMP (standard of care)*	*Authorized*	*Yes*

AxMP =auxiliary medicinal product; CS =corticosteroid; EEA =European Economic Area; ICS =inhaled corticosteroid; IM =intramuscular; IMP =investigational medicinal product; IV =intravenous; LABA =long-acting beta-agonist; LAMA =long-acting muscarinic antagonist; SABA =short-acting beta-agonist; SAMA =short-acting muscarinic antagonist.

[a] *LABA, SABA, LAMA, SAMA, ICS, and CS are not individual products, but classes of medicines, with some classes combined in dual or triple therapy combination inhalers. Classes of medicines are used because an exhaustive list of these products/combinations would not fit into the appendix of this protocol. LABA include, but are not limited to, salmeterol, arformoterol, formoterol, indacaterol, and olodaterol. SABA include, but are not limited to, salbutamol, ipratropium, fenoterol, levalbuterol, albuterol, and terbutaline. LAMA include, but are not limited to, umeclidinium, aclidinium bromide, glycopyrronium bromide, tiotropium, glycopyrrolate, and revefenacin. SAMA include, but are not limited to, ipratropium bromide, and oxitropium bromide. ICS include, but are not limited to, fluticasone propionate, beclomethasone dipropionate, budesonide, ciclesonide, fluticasone furoate, and mometasone furoate. CS (given systemically via the oral, intravenous, or intramuscular route) are a broad class of medicines including various compounds such as prednisolone and dexamethasone, amongst many others. The Sponsor expects that these medicines are given as standard treatment per local regulation, marketing authorization, and treatment guidelines. Approved AxMP highlighted have at least a class that can be matched as per ATC Code (Level 3), and examples of products are provided for an exact match for an example SmPC.*

Appendix 12
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in 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 [a]	NIMP (standard of care)	Approved	*Yes*
SABA [a]	NIMP (standard of care)	Approved	*Yes*
LAMA [a]	NIMP (standard of care)	Approved	*Yes*
SAMA [a]	NIMP (standard of care)	Approved	*Yes*
ICS [a]	NIMP (standard of care)	Approved	*Yes*
CS (oral, IV, IM) [a]	NIMP (standard of care)	Approved	*Yes*

CS = corticosteroid; ICS = inhaled corticosteroid; IM = intramuscular; IMP = investigational medicinal product; *IV = intravenous;* 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] *LABA, SABA, LAMA, SAMA, ICS, and CS are not individual products, but classes of medicines, with some classes combined in dual or triple therapy combination inhalers. Classes of medicines are used because an exhaustive list of these products/combinations would not fit into the appendix of this protocol. LABA include, but are not limited to, salmeterol, arformoterol, formoterol, indacaterol, and olodaterol. SABA include, but are not limited to, salbutamol, ipratropium, fenoterol, levalbuterol, albuterol, and terbutaline. LAMA include, but are not limited to, umeclidinium, aclidinium bromide, glycopyrronium bromide, tiotropium, glycopyrrolate, and revefenacin. SAMA include, but are not limited to, ipratropium bromide, and oxitropium bromide. ICS include, but are not limited to, fluticasone propionate, beclomethasone dipropionate, budesonide, ciclesonide, fluticasone furoate, and mometasone furoate. CS (given systemically via the oral, intravenous, or intramuscular route) are a broad class of medicines including various compounds such as prednisolone and dexamethasone, amongst many others. The Sponsor expects that these medicines are given as standard treatment per local regulation, marketing authorization, and treatment guidelines. Approved NIMP highlighted have at least a class that can be matched as per ATC Code (Level 3), and examples of products are provided for an exact match for an example SmPC.*

Appendix 13
Description of Laboratories for Central Laboratory Testing, Analysis, and Sample Destruction of Study GB44332 in China

The Sponsor delegates the testing, analysis, and destruction of samples for Study GB44332 from China sites to the following China domestic companies:

Testing items	***Central laboratory for testing and analysis***	***Institution for sample destruction***
• *Chemistry panel (serum or plasma): bicarbonate, sodium, potassium, chloride, glucose, urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, and AST* • *Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)* • *Urinalysis: including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria)* • *Serum pregnancy test* • *Serum hsCRP*	*Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd.*	*Shanghai Solid Waste Disposal Co., Ltd.*
• *Serum PK* • *Serum ADA* • *Serum soluble ST2*	*PPD Laboratories (Suzhou) Co., Ltd.*	*Zhangjiagang Huarui Hazardous Waste Disposal Center Co., Ltd.*
• *Blood SNP analysis* [redacted]	*Q Squared Solutions (Beijing) Co.*	*Beijing Ruentex Environment Technology Corp.* *Beijing Solid Waste Flow Co., Ltd.*

ADA =anti-drug antibody; PK =pharmacokinetic; hsCRP =high-sensitivity C-reactive protein; SNP =single nucleotide polymorphism.

Appendix 14
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 2 (9 NOVEMBER 2022)

Protocol GB44332, Version 2 has been amended to include language preferred as part of the harmonized multinational Clinical Trials Regulation (CTR) process and to add an intensive PK study in China. Additionally, the amendment will include additional changes initiated by the Sponsor.

Changes to Version 1 of the protocol, along with a rationale for each change, are summarized below:

- The Cover Page has been updated to include the EU Trial number for CTR and the assigned NCT number (Cover Page).
- Table 2 has been added for intensive pharmacokinetic and biomarker samples that will be collected for some patients enrolling in mainland China (Section 1.3, Table 2).
- Modified intention to treat (mITT) population reference for analysis has been removed from the study objectives and an mITT definition has been instead added in the population statement for the estimand definition study population (Section 3, Table 3).
- Discontinuation from study prior to Week 52 has been removed as an intercurrent event (Section 3, Table 3).
- Safety outcomes have been updated to clarify the safety endpoints that will be evaluated and the definition of adverse events of special interest (Section 3 [Table 4] and Section 8.5.8). In addition, it has been clarified that summary measures include counts and percentages of participants with the adverse event under analysis.
- Study design, end of study definition, and inclusion criteria have been updated to accommodate enrollment of participants in China (Sections 4.1.1, 4.4, 5, 5.1, 9.3.1, and 9.3.4.6).
- The inclusion criteria and on-study maintenance therapy related to standard of care maintenance therapy of chronic obstructive pulmonary disease, has been updated to remove the fluticasone proprionate equivalent minimum dose for inhaled corticosteroid use (Sections 5.1 and 6.1.1).
- Additional clarification has been provided regarding the blinding of the study. Specifically, it has been clarified which individuals or groups of individuals are unblinded in order to fulfill their roles, and details have been added with respect to unblinding of the treatment assignment in case of a medical emergency and for mandatory regulatory reporting of serious, unexpected suspected adverse reactions (Section 6.3.2).

- Medical device complaint language and reporting requirements have been added to clarify how complaints and adverse events should be reported (Section 8.5.9 and Appendix 6).
- Primary estimand and statistical analytical approaches have been clarified (Sections 9.3.2 and 9.3.3).

PROTOCOL AMENDMENT, VERSION 3 (26 MAY 2023)

GB44332 has been amended to include language preferred as part of the harmonized multinational Clinical Trials Regulation (CTR) process and to allow for additional testing at screening where required by local regulations. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- HIV testing has been added as a screening assessment where required by local regulations (Sections 1.3 and 5.2).
- Tuberculosis testing has been added as a screening assessment where required by local regulations (Sections 1.3 and 5.2).
- Safety reporting process has been clarified to align with CTR requirements (Section 8.5.4).
- The safety analysis has been updated to clarify the comparison between the active and control arm (Section 9.3.3.2).

Appendix 15
Abbreviations

Abbreviation or Term	Definition
ADA	anti-drug antibody
AER	annualized exacerbation rate
AHR	airway hyper responsiveness
ATS	American Thoracic Society
AUC	area under the concentration–time curve
BID	twice a day
CAT	COPD Assessment Test
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CT	computed tomography
DAIDS	Division of AIDS
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eDiary	electronic Diary
E-RS:COPD	Evaluating Respiratory Symptoms in COPD
ERS	European Respiratory Society
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
iDMC	independent Data Monitoring Committee
IFN	interferon
IIS	investigator-initiated study
IL-1	interleukin-1
IL-1RL1	interleukin-1 receptor-like 1
IL-33	interleukin-33
IL	interleukin
IM	intramuscular
IMP	investigational medicinal product

Appendix 15: Abbreviations

Abbreviation or Term	Definition
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or Web-based response system
LABA	long-acting beta-agonist
LAMA	long-acting muscarinic antagonist
MACE	major adverse cardiovascular events
mITT	modified intent-to-treat (population)
mMRC	modified Medical Research Council Dyspnea Scale
MN	mobile nursing
NIMP	non-investigational medicinal product
NK	natural killer (cell)
OLE	open-label extension
PD	pharmacodynamic
PDE4	phosphodiesterase 4
PFS-NSD	prefilled syringe with needle safety device
PK	pharmacokinetic
PRO	participant-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	once a day
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
SAMA	*Short-acting muscarinic antagonist*
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SGRQ-C	Saint George's Respiratory Questionnaire–COPD
SNP	single nucleotide polymorphism
SOC	standard of care
Th2	T helper type 2 (cell)
ULN	upper limit of normal
WES	whole-exome sequencing
WGS	whole-genome sequencing
WHO	World Health Organization
WOCBP	women of childbearing potential

Signature Page for Protocol - GB44332 - ASTEGOLIMAB - v5- Global/Core - Publishe
System identifier: RIM-CLIN-630231

Approval Task	[redacted] Company Signatory 08-Nov-2024 10:00:54 GMT+0000