CLINICAL STUDY PROTOCOL

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lebrikizumab/LY3650150 in Participants with Chronic Rhinosinusitis with Nasal Polyps on Background Intranasal Corticosteroids

Short Title: A study to evaluate the efficacy and safety of lebrikizumab in participants with chronic rhinosinusitis with nasal polyps treated with intranasal corticosteroids

PROTOCOL NO. J2T-MC-KGBU

IND Number 167640
EU CT Number 2023-508760-29-00

Sponsor:	Lilly Research Laboratories Eli Lilly and Company Indianapolis, Indiana 46285
Medical Monitor:	PPD Medical Monitor Telephone (24-hour safety hotline): 1-888-483-7729 Fax (24-hour safety hotline fax): 1-888-529-3836
Version of Protocol:	Amendment 3
Date of Protocol:	24 July 2024
Drug Number/Compound Name:	Lebrikizumab
Study Phase:	Phase 3

CONFIDENTIAL

The study will be conducted in compliance with the protocol and according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use harmonised tripartite guideline E6(R2): Good Clinical Practice and applicable regulatory requirements.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lebrikizumab/LY3650150 in Participants with Chronic Rhinosinusitis with Nasal Polyps on Background Intranasal Corticosteroids
Protocol Number	J2T-MC-KGBU
Protocol Date and Version	24 July 2024, Amendment 3

Protocol accepted and approved by:

Medical Director

Claudia Rodriguez Capriles
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46285

DocuSigned by:
Claudia Rodriquez
Signer Name: Claudia Rodriquez
Signing Reason: I approve this document
Signing Time: 24-Jul-2024 | 2:09:16 PM GMT
F797738CAD294FA8939295B099055F1F

Signature _____ Date _____

Protocol Approval – Lead Statistician

Study Title	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lebrikizumab/LY3650150 in Participants with Chronic Rhinosinusitis with Nasal Polyps on Background Intranasal Corticosteroids
Protocol Number	J2T-MC-KGBU
Protocol Date and Version	24 July 2024, Amendment 3

Protocol accepted and approved by:

Lead Statistician

Fangyi Zhao
Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46285

DocuSigned by:
Fangyi Zhao

Signature: _____ Date: _____

Signature
Signing Name: Fangyi Zhao
Signing Reason: I approve this document
Signing Time: 24-Jul-2024 | 12:35:10 PM EDT
CAB7641ACFAA4C6D83CEE963FB23A88B

Declaration of Investigator

I have read and understood all sections of the protocol titled "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lebrikizumab/LY3650150 in Participants with Chronic Rhinosinusitis with Nasal Polyps on Background Intranasal Corticosteroids" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical study in accordance with the Final Protocol Amendment 3, dated 24 July 2024, the ICH harmonised tripartite guideline E6(R2): GCP and all applicable government regulations. I will not make changes to the protocol before consulting with Eli Lilly and Company or implement protocol changes without IRB/IEC approval, except to eliminate an immediate risk to participants. I agree to administer study treatment only to participants under my personal supervision or the supervision of a subinvestigator.

I will not supply the study treatment to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this study or publish results of the study without authorization from Eli Lilly and Company.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Protocol Amendment Summary of Changes

Protocol Version History	
Protocol Version	**Date**
Amendment 3	24 July 2024
Amendment 2	01 July 2024
Amendment 1	08 December 2023
Original Protocol	17 November 2023

Amendment 3 (24 July 2024**)**

Overall Rationale for the Amendment: The main rationale for this amendment is to align with recommendations from the FDA. Appendices were also added for South Korea and Taiwan for country-specific requirements.

Changes from Amendment 2 (01 July 2024) to Amendment 3 (24 July 2024) are summarized in the following table.

Section # and Name	Description of Change	Brief Rationale
Global	Updated study title to removed “adult” to reflect that both adult and adolescent participants will be enrolled.	Updated title for the inclusion of adolescents.
1.1 Protocol Synopsis, 3.1 Objectives and Endpoints	Updated objectives and endpoints to describe analyses being conducted on data from adolescents. Updated key secondary endpoint related to FEV_1 to clarify participants with asthma at baseline.	Updated text for the inclusion of adolescents and clarity.
1.1 Protocol Synopsis, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design	Updated overall study design and study rationale to include information on adolescent participants.	Updated text for the inclusion of adolescents.
1.1 Protocol Synopsis, 6.3 Assignment to Investigational Product	Added “All eligible adolescents will be assigned to the lebrikizumab Q2W/Q4W treatment on an open-label basis.”	Updated text for the inclusion of adolescents.
1.1 Protocol Synopsis, 9 Statistical Considerations, 9.3 Sample Size Determination, 9.4 Analysis Sets, 9.5 Statistical Analysis Methodology, 9.8 Multiple Comparisons and Multiplicity	Added text in the statistical sections for the inclusion of adolescents.	Updated text for the inclusion of adolescents.
1.2 Study Schema	Added note for the study design for the inclusion of adolescents.	Updated text for the inclusion of adolescents.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Updated SoA to include the following for adolescents: assent, collection of height throughout the study, pregnancy testing for all adolescent females, review of vaccination status, review of documentation for ruling out cystic fibrosis and primary ciliary dyskinesis, redefinition of "randomization" as "assignment to treatment," and updated footnotes to reflect adolescent updates. Also updated SoA for all patients to define baseline collection of substance use and clarify genetic sampling.	Updated text for the inclusion of adolescents. Updated text for clarity on collection of substance use and genetic sample.
2.2.1 Pathobiology and Clinical Manifestations of CRSwNP, 2.2.2 Treatment of CRSwNP, 2.2.3 Lebrikizumab, 14 References	Updated to provide additional background information and references for treatment of adolescents.	Updated text for the inclusion of adolescents.
2.3.2 Risk Assessment	Updated risk assessment to include adolescents and for clarity..	Updated text for the inclusion of adolescents and clarity.
3.1 Objectives and Endpoints	Updated other secondary endpoints to clarify mean score for Patient Global Impression of Change.	Updated text for clarity.
4.3 Justification of Dose	Added "Data from studies of lebrikizumab adolescents weighing ≥40kg with AD and asthma indicate that efficacy and safety findings in adolescents are similar to those observed in adults (Paller 2023; Szefler 2022)."	Updated text for the inclusion of adolescents.
5.1 Inclusion Criteria	Updated criteria 1 and 9 to include adolescents. Revised criteria 3, 5, 7, and 8 for clarity.	Updated text for the inclusion of adolescents and clarity.
5.2 Exclusion Criteria	Updated criteria 14 and 15 to include adolescents. Revised criteria 9, 22, and 33 for clarity.	Updated text for the inclusion of adolescents and clarity.
6.1 Study Treatments Administered	Added table notes for enrollment of adolescents and updated Table 6-2 and 6-3 for clarity.	Updated text for the inclusion of adolescents and clarity.
6.2 Preparation, Handling, Storage, and Accountability	Updated background medication responsibility for clarity.	Updated text for clarity.

Section # and Name	Description of Change	Brief Rationale
6.3.1 Other Supplies	Updated text to explain that the sponsor will supply the required background medication, mometasone furoate.	Updated text for the inclusion of adolescents.
6.4 Blinding	Added text for adolescent participants.	Updated text for the inclusion of adolescents.
6.10.2.1 Prohibited Concomitant Medications	Added parameters for oral decongestant use.	Updated text for clarity.
6.10.2.2 Allowed Medications	Added parameters for oral decongestant and anesthetic use.	Updated text for clarity.
7.2.2 Withdrawal of Inadvertently Enrolled Participants	Updated text for clarity.	Updated text for clarity.
8.1.1 Informed Consent and Assent Procedure	Updated text to include assent for adolescents.	Updated text for the inclusion of adolescents.
8.2 Efficacy Assessments	Updated efficacy assessments to include "Adolescent participants should enter their responses into the ePRO devices (eDiary and tablet) independently but may have parental supervision if needed."	Updated text for the inclusion of adolescents.
8.2.2 Endoscopic NPS	Removed the word "flexible" regarding the type of nasal endoscope to be used.	Updated text to allow either flexible or rigid endoscope, consistent with standard practice.
8.3.4 Height	Updated to include "Height for adolescents will also be measured whenever vital signs and weight are assessed according to the SoA (Table 11) to evaluate participants' growth over time."	Updated text for the inclusion of adolescents.
8.3.7.8 Close Hepatic Monitoring	Added "In younger adolescents, special care should be taken to minimize the volume of blood taken during hepatic monitoring."	Updated text for the inclusion of adolescents.
8.4 Pregnancy	Updated text to include female adolescents.	Updated text for the inclusion of adolescents.
8.6.1 Exploratory Blood and Nasal Biomarkers	Updated blood and nasal biomarker text for clarity.	Updated text for clarity.
8.7 Immunogenicity Assessments	Updated text to clarify immunogenicity testing.	Updated text for clarity.

Section # and Name	Description of Change	Brief Rationale
11.3 Participant Information and Consent	Updated to include requirements for adolescent consent.	Updated text for the inclusion of adolescents.
15.1 Contraceptive Guidance	Updated to include adolescent females.	Updated text for the inclusion of adolescents.
15.6 Provisions for Changes in Study Conduct During Exceptional Circumstances	Updated informed consent information to include adolescents.	Updated text for the inclusion of adolescents.
15.7 Country-specific Requirements – South Korea	Added Appendix 15.7 to describe South Korea country-specific requirements.	Updated text for country-specific requirements.
15.8 Country-specific Requirements – Taiwan	Added Appendix 15.8 to describe Taiwan country-specific requirements.	Updated text for country-specific requirements.
15.9 Protocol Amendment 2 Summary of Changes	Added Protocol Amendment 2 Summary of Changes.	Added appendix for clarity.

Note: Amendment 2 updated the protocol based on required changes per the EU CTA. Changes from Amendment 1 (08 December 2023) to Amendment 2 (01 July 2024) are summarized in Appendix 15.9.

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List of Abbreviations and Definition of Terms

Abbreviation	Expanded Forms
ACQ-6	Asthma Control Questionnaire-6
AD	atopic dermatitis
ADA	antidrug antibodies
AE	adverse event
AERD	aspirin-exacerbated respiratory disease
AESI	adverse event of special interest
BID	twice daily
CFBL	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CRO	contract research organization
CRSwNP	chronic rhinosinusitis with nasal polyps
CT	computed tomography
eCOA	electronic clinical outcome assessments
eCRF	electronic case report form
eDiary	electronic diary
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GDPR	EU General Data Protection Regulation
HBcAb	Hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	investigator’s brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroids
IEC	Institutional Ethics Committee

Abbreviation	Expanded Forms
Ig	immunoglobulin
IL	interleukin
INCS	intranasal corticosteroids
IP	investigational product
IRB	Institutional Review Board
ISR	injection site reaction
ITT	Intent-to-Treat
IWRS	interactive web response system
LMK	Lund Mackay score
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
NCS	nasal congestion score
NP	nasal polyps
NPIF	nasal peak inspiratory flow
NPS	nasal polyp score
PBO	placebo
PD	pharmacodynamic/s
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic/s
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
SAE	serious adverse event
SAF	Safety (Analysis Set)
SAP	statistical analysis plan
SCIT/SLIT	subcutaneous immunotherapy/sublingual immunotherapy
SCS	systemic corticosteroids
SD	standard deviation
SFU	safety follow-up

Abbreviation	Expanded Forms
SNOT-22	22-item Sino-Nasal Outcome Test
SoA	Schedule of Activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TE ADA	treatment-emergent antidrug antibodies
TEAE	treatment-emergent adverse event
UPSIT	University of Pennsylvania Smell Identification Test
VAS	visual analog scale
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential
WPAI+CIQ:CRSwNP	Work Productivity and Activity Impairment plus Classroom Impairment Questions: chronic rhinosinusitis with nasal polyps

1 Protocol Summary

1.1 Protocol Synopsis

Protocol Number: J2T-MC-KGBU

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lebrikizumab/LY3650150 in Participants with Chronic Rhinosinusitis with Nasal Polyps on Background Intranasal Corticosteroids

Short Title: A study to evaluate the efficacy and safety of lebrikizumab in participants with chronic rhinosinusitis with nasal polyps treated with intranasal corticosteroids

Sponsor: Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46285

Indication: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

EU CT Number: 2023-508760-29-00

Rationale: To date, systemic corticosteroids (SCS) and surgery have been used to treat chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), which provide short-term relief and/or disease recurrence. Lebrikizumab is a monoclonal antibody that selectively inhibits interleukin (IL)-13 signaling. Blocking IL-13 signaling is expected to be beneficial for treating CRSwNP where IL-13 is a central cytokine involved in disease pathogenesis.

Currently, dupilumab, omalizumab, and mepolizumab have been approved for the treatment of CRSwNP in adults, and despite these treatments, a proportion of patients still require rescue with SCS or surgery. There are currently no biologic treatments approved for CRSwNP in adolescents.

Lebrikizumab is being evaluated in this study (J2T-MC-KGBU), a pivotal Phase 3, multinational, multicenter, randomized, double-blind, placebo (PBO)-controlled, parallel group study to evaluate the efficacy and safety of lebrikizumab compared to PBO in participants with CRS with bilateral nasal polyps (NP) who receive background therapy with intranasal corticosteroids (INCS). This 72-week study will evaluate the efficacy of lebrikizumab in reducing the signs and symptoms of CRS with bilateral NP. The primary cohort of participants will be adults at least 18 years of age. The study will also be open to adolescent participants at least 12 years of age and weighing at least 40 kg who will all be assigned to lebrikizumab treatment.

Objectives, Endpoints, and Estimands:

All objectives and endpoints in the table will be analyzed for the adult cohort of participants. All endpoints in the table will also be collected in the adolescent cohort but will be summarized separately for that cohort using descriptive statistics and listings.

Objectives	Endpoints
Primary:	
• To evaluate the efficacy of lebrikizumab 250 mg Q2W compared to PBO in reducing nasal congestion severity and endoscopic nasal polyp score on background INCS at Week 24	• Mean CFBL at Week 24 in participant reported NCS severity • Mean CFBL at Week 24 in endoscopic NPS
Key Secondary:	
• To evaluate the efficacy of lebrikizumab in reducing the signs and symptoms in participants	• Mean CFBL at Week 56 in endoscopic NPS • Mean CFBL at Week 56 in a participant reported NCS • Mean change in opacification of sinuses measured by the LMK from baseline to Weeks 24 and 56 • Mean change in FEV_1 from baseline to Weeks 24 in patients with asthma at baseline • Mean CFBL in severity of loss of smell at Weeks 4, 24, and 56 • Mean CFBL in postnasal drip at Weeks 24 and 56 • Proportion of and time-to-event for participants receiving systemic corticosteroids, and/or approved biologics for CRSwNP rescue use, and/or planned surgery of NP during study treatment period
Safety:	
• To describe the safety and tolerability of lebrikizumab	• Incidence of adverse events and serious adverse events; postbaseline values and changes over time of

Objectives	Endpoints
	clinical laboratory evaluations, and vital signs

Note: Adolescent participants' efficacy and safety data will be summarized separately from that of the adult participants.

Abbreviations: CFBL = change from baseline; CRSwNP = chronic rhinosinusitis with nasal polyps eDiary = electronic diary; FEV_1 = forced expiratory volume in 1 second; IgE = immunoglobulin E; LMK = Lund Mackay score; NCS = nasal congestion score; NP = nasal polyps; NPS = nasal polyp score; PROs = patient-reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; Q2W = every 2 weeks; SoA = Schedule of Activities; WPAI+CIQ:CRSwNA = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment: chronic rhinosinusitis with nasal polyps.

Estimand: The primary estimand is a hybrid estimand representing the primary clinical question of interest: what is the difference between treatment conditions (lebrikizumab versus PBO), in the target adult patient population, without NP surgery, change to another approved biologic therapy, or long-term use of SCS or nasal saline lavage with corticosteroids (>10 days), and regardless of the study treatment discontinuation or short-term use of SCS?

Change from baseline (CFBL) in endoscopic nasal polyp score (NPS) and CFBL in nasal congestion score (NCS) severity using difference in population means will be compared between participants treated with lebrikizumab and PBO in combination with background standard of care, regardless of treatment discontinuation or short-term use of SCS treatment. Nasal polyp surgery, change to another approved biologic therapy, or long-term use of SCS or nasal saline lavage with corticosteroids will be considered as treatment failures. In the case of treatment failure, endoscopic NPS and NCS severity values will be replaced with the worst possible scores.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria: Adult participants will be ≥18 years of age at time of consent; with physician-diagnosed CRS with bilateral NP; had prior treatment with SCS for CRS or CRSwNP within the last 2 years; prior surgery for NP, or both; and a bilateral endoscopic NPS of at least 5 out of 8 with a minimum score of 2 in each nasal cavity performed at screening (Visit 1) and baseline (Visit 3). Adolescent participants ≥12 to <18 years of age and weighing ≥40 kg at time of Visit 1 will also be allowed to enroll.

Exclusion Criteria: Participants will be excluded if they have received a dose of lebrikizumab; are currently enrolled in any other clinical study involving an investigational drug or any other type of medical research judged not to be scientifically or medically compatible with this study; have been treated with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to Visit 3; have a known hypersensitivity to any component of lebrikizumab or its excipients; or have a contraindication or intolerance to mometasone furoate.

Study Design: This is a Phase 3, multinational, multicenter, double-blind, PBO-controlled, parallel group, randomized clinical study to evaluate the efficacy and safety of lebrikizumab in participants with CRS and bilateral NP who receive background therapy with INCS.

This study has 4 study periods:

- Screening (up to 30 days)
- Run-in (4 weeks)
- Randomized treatment (56 weeks), which includes an induction period (24 weeks; Week 0 to Week 24) and a maintenance period (32 weeks; Week 24 to Week 56)
- Safety follow-up (SFU) (8 weeks), starting after the study site visit at Week 56. For participants who complete the final maintenance visit at Week 56, SFU (Visit 801) will occur at Week 64 (12 weeks after the last dose scheduled at Week 52). If a participant withdraws from the study early, SFU (Visit 801) will be scheduled to occur 12 weeks after the last dose received.

Adult participants meeting the inclusion and exclusion criteria will be randomly assigned to receive either lebrikizumab or matching PBO at baseline (Visit 3). All adolescent participants will be assigned to lebrikizumab on an open-label basis using the same dose regimen as per adults assigned to Q2W/Q4W.

Randomization for adult participants will use block randomization with fixed block size and will be stratified by the following factors:

- Asthma and/or aspirin-exacerbated respiratory disease (AERD) versus no asthma/no AERD
- Prior NP surgery versus no prior NP surgery
- Geographic region (North America, Europe, rest of the world)

Adult participants, investigators, and study site staff will be fully blinded to treatment arm. Adolescent participants will receive treatment on an open-label basis.

Description of Study Treatment: Adult participants will receive lebrikizumab or matching PBO via subcutaneous injection. Adult participants will be randomly assigned 1:1:1 using an interactive web response system to the following treatment arms:

- Lebrikizumab every 2 weeks (Q2W)/every 4 weeks (Q4W) Arm: Lebrikizumab 500 mg loading dose at Week 0 and Week 2, followed by lebrikizumab 250 mg Q2W through Week 24 (induction period) and then lebrikizumab 250 mg Q4W through Week 56 (maintenance period)
- Lebrikizumab Q2W/every 8 weeks (Q8W) Arm: Lebrikizumab 500 mg loading dose at Week 0 and Week 2, followed by lebrikizumab 250 mg Q2W through Week 24 (induction period) and then lebrikizumab 250 mg Q8W through Week 56 (maintenance period)
- PBO Arm: PBO Q2W through Week 24 (induction period) and then PBO Q4W through Week 56.

Enrollment of adolescents will be on an open-label basis, with all adolescents assigned to the lebrikizumab Q2W/Q4W treatment arm.

All participants will receive intranasal mometasone furoate at the start of the run-in period through Week 56. Participants may continue mometasone furoate during the SFU period at the discretion of the investigator.

Duration of Treatment: The maximum planned duration of study participation for each participant will be up to approximately 72 weeks.

Efficacy Assessments:

Primary Efficacy Assessments: The primary objective will be evaluated by 2 endpoints: mean CFBL to Week 24 in a participant reported NCS, and mean CFBL to Week 24 in endoscopic NPS.

NCS Severity at Week 24: NCS severity is rated by study participants using a 4-point scale (range from 0 to 3), where 0 corresponds to no symptoms and 3 corresponds to severe symptoms, and is also a home-based electronic clinical outcome assessment. Study participants are asked to record their nasal congestion symptom severity, at its worst, for the previous 24 hours using a daily electronic diary. The NCS at each analysis time point will be the average score over the previous 14 days.

Endoscopic NPS at Week 24: The endoscopic NPS is assessed by a centralized, blinded, independent review of nasal endoscopy video recordings. The total score is the sum of the right and left nasal cavity scores. For each nasal cavity, endoscopic NPS is graded based on polyp size from 0 to 4, where 0 = no polyps and 4 = large polyps. Endoscopic NPS will be calculated as the average of scores from 2 trained physician assessors reviewing video recordings of nasal endoscopies where assessors are blinded to participants' IP assignment. An adjudication process will be in place for discordant results between the 2 assessors.

Key Secondary Efficacy Assessments

The key secondary objective will be evaluating the efficacy of lebrikizumab in reducing the signs and symptoms of CRS with bilateral NP from baseline to Week 24 and Week 56. Key secondary efficacy assessments are the following: endoscopic NPS and NCS severity; opacification of sinuses; forced expiratory volume in 1 second (FEV_1); severity of loss of smell; postnasal drip; and proportion and time-to-event for participants receiving SCS,

approved biologics for CRSwNP rescue use, and/or planned surgery of NP during study treatment.

Other Secondary Efficacy Assessments

Other secondary efficacy assessments include patient-reported outcomes (PROs).

Exploratory assessments will include the evaluation of the pharmacokinetic and pharmacodynamic profiles of lebrikizumab and to analyze genetic variation to drug response (optional).

Pharmacokinetic and/or Pharmacodynamic Assessments: At the visits presented in the Schedule of Activities (SoA), venous blood samples will be collected to determine the serum concentrations of lebrikizumab.

Blood and nasal samples will be collected to assess nasal and blood markers, and immunoglobulin E during lebrikizumab treatment.

Immunogenicity Assessments: At the visits presented in the SoA, predose venous blood samples will be collected to determine the antibody production against lebrikizumab.

Safety Assessments: Safety assessments will include the collection and reporting of adverse events (AEs), serious AEs, AEs of special interest, weight, vital signs, clinical laboratory tests, injection site reactions, systemic hypersensitivity reactions, eosinophil-related disorders, hepatic safety monitoring, and serious and opportunistic infections. Growth will also be assessed for adolescent participants.

Details of Applicable Monitoring Committee: Not applicable to this study.

Sample Size: Approximately 1020 adult participants will be screened to achieve 510 randomly assigned to IP, with 170 adult participants in the PBO group and 340 adult participants across the 2 lebrikizumab dose groups. This planned sample size was calculated based on the treatment effect observed in SINUS-24 and SINUS-52 and uses the assumption that the mean difference in CFBL in NCS severity between lebrikizumab and PBO is 0.62 with common standard deviation (SD) 1.0, and the mean difference in CFBL in endoscopic NPS is 1.48 with common SD 2.1. Assuming normal distribution and no negative correlation between the 2 endpoints and 20% dropout rate, a sample size of 170 participants per arm is

expected to be sufficient to provide a combined power of 99% using a 2-sided t test with alpha of 0.01 for changes from baseline in NCS severity and endoscopic NPS at Week 24. In addition to the co-primary endpoints, the sample size also allows sufficient power for the key secondary endpoint of time-to-event for participants receiving systemic corticosteroids, and/or approved biologics for CRSwNP rescue use, and/or planned surgery. Assuming the probability of having such rescue events during study treatment period is 27% in the placebo group, and is 10% in the lebrikizumab group, with 170 patients per arm, the study will have approximately 90% power to detect a hazard ratio of 0.35 between the treatment groups using a 2-sided log-rank test with alpha of 0.01.

There will be no target sample size for the adolescent population. The study design will allow as many adolescents to be enrolled as possible as long as the adult enrollment period is still open. Any adolescent participants enrolled will not contribute to the target number for adult participants.

Statistical Methods: Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarized using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings. All confidence intervals presented will be 99% (2-sided) confidence intervals for primary and key secondary endpoints.

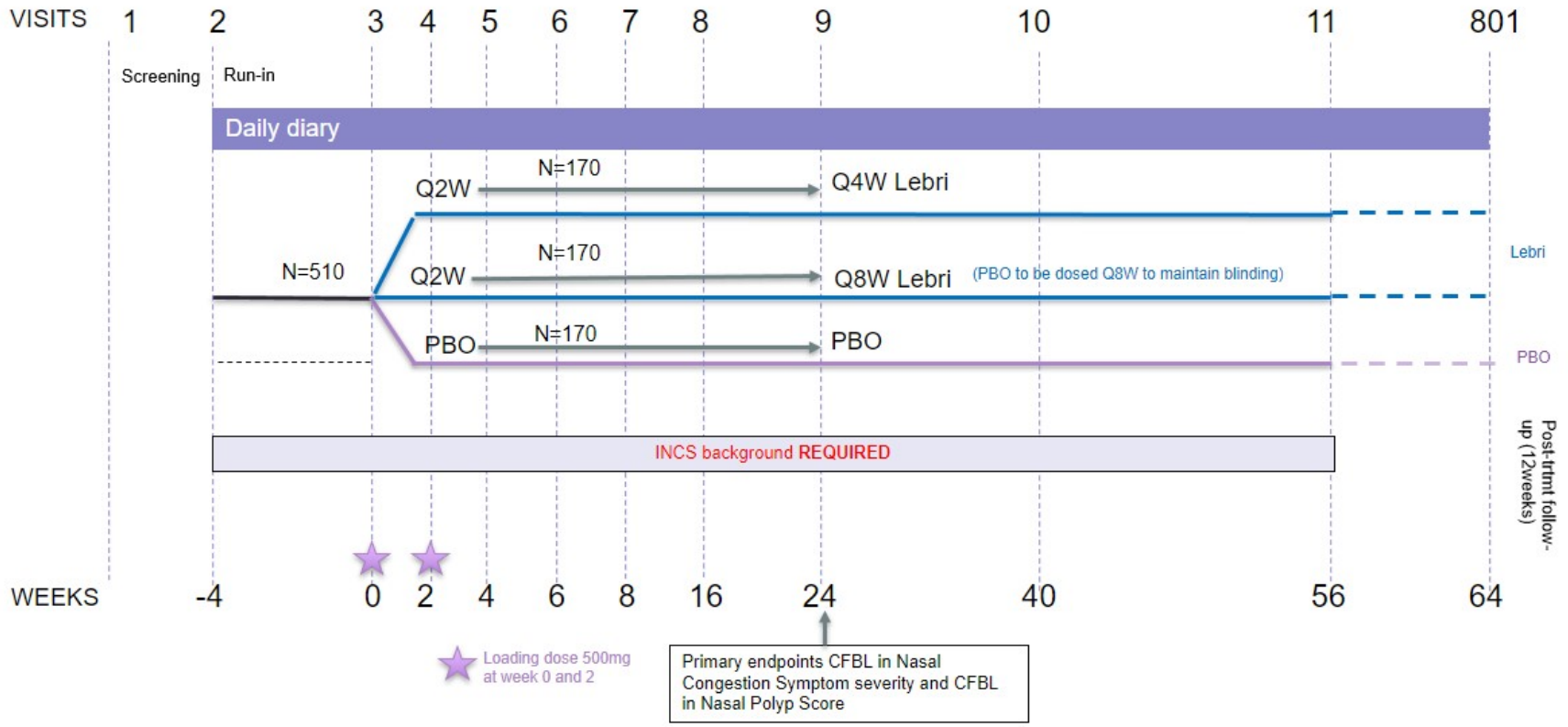
Full details of the statistical analyses, methods, and data conventions will be described in the statistical analysis plan.

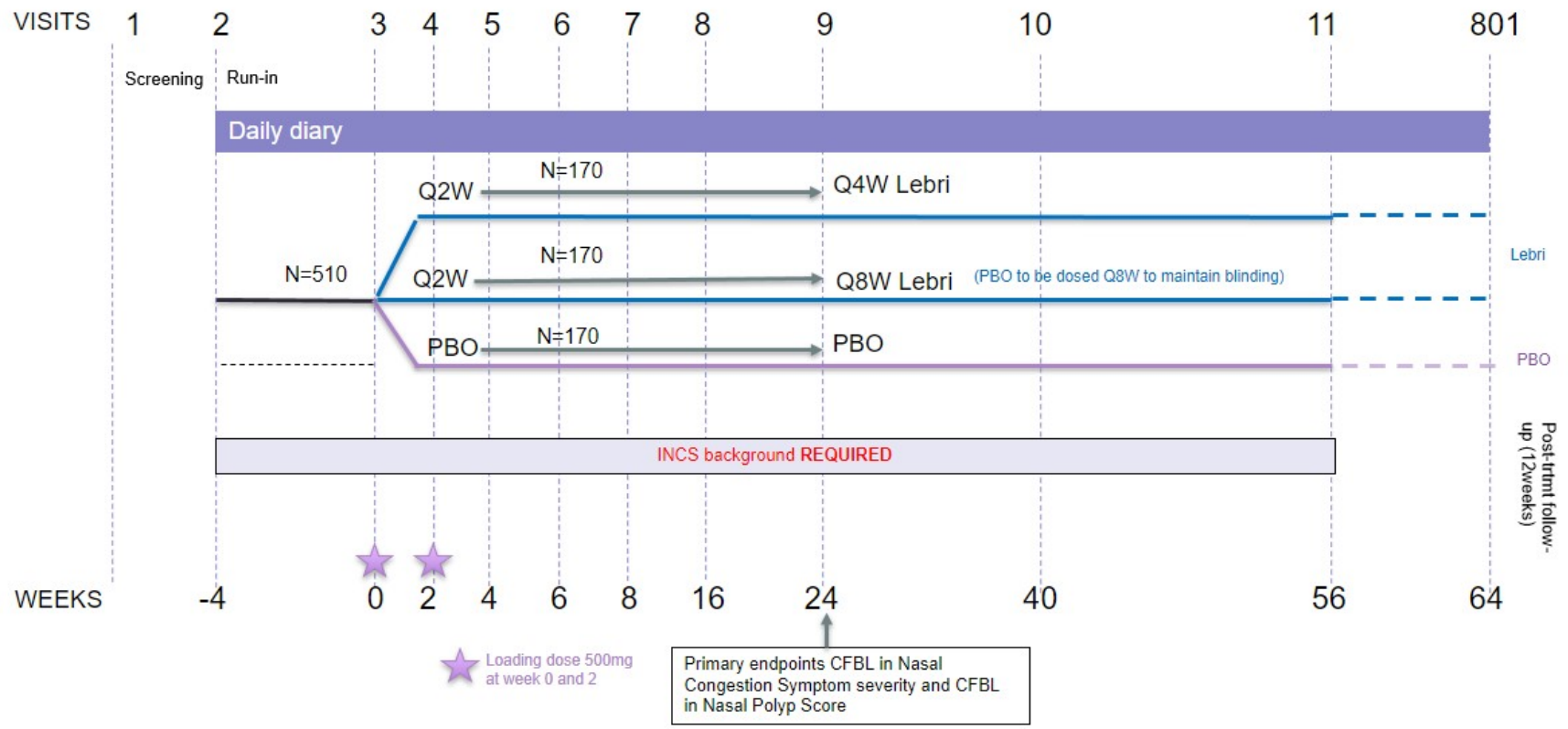
Adolescent data will be summarized using descriptive statistics and listings.

1.2 Study Schema

Study design is presented in Figure 1-1.

Figure 1-1 Study Design





Note: Adolescent patients will receive treatment in the Lebri Q2W/Q4W arm on an open-label basis and will be separate from the 510 adult participants in this study.

Abbreviations: CFBL = change from baseline; INCS = intranasal corticosteroids; Lebri = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks.

1.3 Schedule of Activities

The SoA described in Table 1-1 will be followed for all participants enrolled in this study.

Table 1-1 Schedule of Activities

CRSwNP 72 Week	Screening	Run-In	Randomized[a] Treatment Period								EOT/ET	UV	SFU
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**UV[b]**	**801**
Weeks from randomization	**W-8 to W-4**	**W-4 to W0**	**Baseline**	**W2**	**W4**	**W6**	**W8**	**W16**	**W24**	**W40**	**W56**	**NA**	**W64 or 12 weeks after last dose**
Days from randomization	**D-58 to D-28**	**D-28 to D0**	**D0**	**D14**	**D28**	**D42**	**D56**	**D112**	**D168**	**D280**	**D392**	**NA**	**D448**
Activity Visit interval tolerance (days)	**--**	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**NA**	**±5**
Informed consent (and assent for adolescents)	X												
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X		X
Medical history including prior surgeries, prior medications, and prior eye disease history	X												
Substance use (alcohol, nicotine containing products, tobacco)	X												
Vital signs[c] and weight measurement	X	X	X		X				X	X	X	X	X
Prior treatments for CRSwNP[d]	X												
Participant demographics	X												
Physical examination (includes height for adults)	X												
Height for adolescents	X		X		X				X	X	X	X	X
Review vaccination status for adolescents[e]	X												
Review documentation for ruling out cystic fibrosis and primary ciliary dyskinesia for adolescents[f]	X												
Inclusion and exclusion criteria	X		X										
Chest x-ray[g]	X												
Treatment													
Randomization (refers to treatment assignment in IWRS)			X										

CRSwNP 72 Week	Screening	Run-In	Randomized[a] Treatment Period								EOT/ET	UV	SFU
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**UV[b]**	**801**
Weeks from randomization	**W-8 to W-4**	**W-4 to W0**	**Baseline**	**W2**	**W4**	**W6**	**W8**	**W16**	**W24**	**W40**	**W56**	**NA**	**W64 or 12 weeks after last dose**
Days from randomization	**D-58 to D-28**	**D-28 to D0**	**D0**	**D14**	**D28**	**D42**	**D56**	**D112**	**D168**	**D280**	**D392**	**NA**	**D448**
Activity Visit interval tolerance (days)	**--**	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**NA**	**±5**
Dispense and administer IP at clinic[h]			X	X	X	X	X	X	X	X			
Dispense IP for away dosing[h]							X	X	X	X			
Train participant and/or caregiver on investigational product administration							X						
Study site dispensing background medication		X	X	X	X	X	X	X	X	X	X		
Procedures													
Nasal endoscopy (NPS)[i]	X		X		X		X	X	X	X	X	X	
CT scan (sinus) with LMK[j]			X						X		X		
Spirometry[k,r]	X		X	X	X		X	X	X	X	X		
UPSIT (Smell Test)			X	X	X			X	X		X		
NPIF[r]	X	X	X	X	X	X	X	X	X	X	X		
Participant eDiary[l]													
Participant eDiary dispensed[l]		X											
Participant eDiary compliance check[m]			X	X	X	X	X	X	X	X	X	X	
Participant eDiary return											X		
Patient-Reported Outcomes/Health-Related Quality of Life (electronic device, site-based)													
VAS of CRS			X	X	X		X		X		X	X	
SNOT-22			X		X		X		X	X	X	X	
ACQ-6[n]			X		X				X		X	X	
EQ-5D-5L			X						X		X	X	
WPAI+CIQ:CRSwNP			X						X		X	X	

CRSwNP 72 Week	Screening	Run-In	Randomized[a] Treatment Period								EOT/ET	UV	SFU
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**UV[b]**	**801**
Weeks from randomization	**W-8 to W-4**	**W-4 to W0**	**Baseline**	**W2**	**W4**	**W6**	**W8**	**W16**	**W24**	**W40**	**W56**	**NA**	**W64 or 12 weeks after last dose**
Days from randomization	**D-58 to D-28**	**D-28 to D0**	**D0**	**D14**	**D28**	**D42**	**D56**	**D112**	**D168**	**D280**	**D392**	**NA**	**D448**
Activity Visit interval tolerance (days)	**--**	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**NA**	**±5**
PROMIS Short Form v1.0 – Anxiety 8a			X						X		X	X	
PROMIS Short Form v1.0 – Depression 8a			X						X		X	X	
PGI-S: nasal congestion			X	X	X	X	X	X	X	X	X	X	
PGI-S: loss of smell			X	X	X	X	X	X	X	X	X	X	
PGI-S: postnasal drip			X	X	X	X	X	X	X	X	X	X	
PGI-C: nasal congestion									X		X	X	
PGI-C: loss of smell									X		X	X	
PGI-C: postnasal drip									X		X	X	
Safety													
Adverse events[o]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Record rescue medication intervention				X	X	X	X	X	X	X	X	X	X
Laboratory Testing													
Pregnancy test (for WOCBP and all female adolescents)[p]	X		X		X		X	X	X	X	X		X
Hematology/clinical chemistry laboratory	X		X		X		X	X	X	X	X		
Urinalysis	X								X		X		
HCV, HBV, HIV tests	X												
HBV DNA[q]	X							X	X	X	X		
Immunogenicity (ADA) sample			X		X			X	X		X		X
Total immunoglobulin E			X		X			X	X		X		

CRSwNP 72 Week	Screening	Run-In	Randomized[a] Treatment Period								EOT/ET	UV	SFU
Visit number	1	2	3	4	5	6	7	8	9	10	11	UV[b]	801
Weeks from randomization	W-8 to W-4	W-4 to W0	Baseline	W2	W4	W6	W8	W16	W24	W40	W56	NA	W64 or 12 weeks after last dose
Days from randomization	D-58 to D-28	D-28 to D0	D0	D14	D28	D42	D56	D112	D168	D280	D392	NA	D448
Activity Visit interval tolerance (days)	--	--	±3	±3	±3	±3	±3	±3	±3	±5	±5	NA	±5
Pharmacokinetics[s]			X		X			X	X	X	X		X
TB assessment (country-specific)[t]	X												
Stored Samples													
Exploratory blood sample biomarkers			X		X			X	X		X		
Exploratory nasal sample biomarkers			X		X			X	X		X		
Genetics sample[u]			X										

Abbreviations: ACQ-6 = Asthma Control Questionnaire-6; ADA = antidrug antibodies; AERD = aspirin-exacerbated respiratory disease; CRS = chronic rhinosinusitis; CRSwNP = chronic rhinosinusitis with nasal polyps; CT = computed tomography; EOT = end of treatment; EQ-5D-5L = EuroQol 5-Dimension 5-Level; ET = early termination; HBV = hepatitis B virus; HBcAb = Hepatitis B antibody; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IP = investigational product; IWRS = interactive web response system; LMK = Lund McKay score; NPIF = Nasal Peak Inspiratory Flow; NPS = nasal polyp score; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; SFU = safety follow-up; SoA = Schedule of Activities; SNOT-22 = 22-item sino-nasal outcome test; TB = tuberculosis; UPSIT = University of Pennsylvania Smell Identification Test; UV = unscheduled visit; VAS = Visual Analog Scale; WOCBP = women of childbearing potential; WPAI+CIQ:CRSwNP = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment: chronic rhinosinusitis with nasal polyps.

a. Randomization will take place at Visit 3 (baseline) and stratified based on 3 factors: asthma and/or AERD versus no asthma/no AERD, prior nasal polyp surgery versus no prior nasal polyp surgery, geographic region (North America, Europe, rest of the world). Participants will be randomly assigned 1:1:1 using an IWRS to the treatment arms presented in Section 4.1. Eligible adolescent participants will automatically be assigned to the lebrikizumab Q2W/Q4W arm.

b. UVs may be conducted to assess efficacy (PROs) and safety before starting any rescue medication (Section 6.10.3); follow the SoA for procedures required in this scenario. UVs for all other purposes will include activities and procedures at investigator's discretion (see Section 8 for details).

c. Includes measurements of blood pressure, pulse, body temperature, and respiratory rate.

d. Includes review of medications and procedures.

e. The investigator should assess if adolescent participant is up to date with immunizations following the local guidelines for vaccination prior to enrolling into the study. For adolescents who are under vaccinated, the investigator should document the benefit/risk rationale for enrolling the participants in the study.

f. The investigator should assess if adolescent participants have cystic fibrosis (CF) and ciliary dysknesia (PCD) prior to enrolling into the study. The presence of these diagnoses associated with NP will be exclusionary and documentation for ruling them out is required before enrollment.

g. Chest x-ray is required for participants at screening, unless one has been performed in the previous 12 months and the x-ray and the report is available. For countries that require an x-ray for TB assessment, follow local guidelines (Section 8.3.7.1).

h. Participants who are not comfortable self-administering IP away from the study site may come to the study site for administration according to the "away" administration schedule (Table 6-2 and Table 6-3). Refer to Section 6.1 for details on IP administration.

i. The endoscopic NPS is assessed by a centralized, blinded, independent review of nasal endoscopy video recordings (Section 8.2.2).

j. CT scan will be performed at the ET visit if no postbaseline CT scan had been done.

k. Spirometry screening for all participants. Any time point after screening is ONLY for participants with asthma (Section 8.2.4). Spirometry should be performed after withholding the last dose of short-acting bronchodilators for at least 6 hours. If the participant has not followed this instruction, their spirometry measurements for that visit should be rescheduled.

l. The eDiary will be completed by the participants around the same time each day (preferably in the morning) starting from run-in (Visit 2), and participants will be asked to record the severity of their nasal congestion, loss of smell, postnasal drip, loss of taste, and facial pain/pressure, and rhinorrhea at its worst for the previous 24 hours using their eDiaries (Section 8.2.1, Section 8.2.5, Section 8.2.6, and Section 8.2.8,).

m. Includes review of dosing eDiaries including background therapy and investigational product injections taken.

n. ACQ-6 test will be performed in participants who have asthma only.

o. Includes assessments of all AEs. AEs will be assessed from the time the participant signs the ICF and up until participation in the study has ended (Section 8.3.1).

p. Pregnancy tests will be conducted only for individuals of childbearing potential and all female adolescents: serum testing at screening and urine testing at subsequent visits prior to administering any IP. Refer to Section 8.4 for details on reporting positive pregnancy test results obtained away from the study site. Additional pregnancy tests (beyond those required by the SoA) should be performed at any time during the study if a menstrual period is missed or there is clinical suspicion of pregnancy. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

q. If HBsAg is negative and HBcAb is positive at screening, further testing for HBV DNA is required (Section 7.1, Section 7.1.2, Section 7.2.1, and Section 8.3.7.6, and Appendix 15.2 and Appendix 15.4).

r. NPIF and spirometry should be performed prior to endoscopy.

s. Blood samples will be collected before dosing of IP on a dosing day.

t. For countries that require an additional TB assessment (ie, QuantiFERON), local guidelines will be followed.

u. Genetic samples will be collected for exploratory research where local regulations allow (Section 8.9).

2 Introduction

2.1 Study Rationale

To date, systemic corticosteroids (SCS) and surgery have been used to treat chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), which provide short-term relief and/or result in disease recurrence. Lebrikizumab is a monoclonal antibody that selectively inhibits interleukin (IL)-13 signaling. Blocking IL-13 signaling is expected to be beneficial for treating CRSwNP where IL-13 is a central cytokine involved in disease pathogenesis. Currently, dupilumab, omalizumab, and mepolizumab have been approved for the treatment of CRSwNP in adults, and despite these treatments, a proportion of patients still require rescue with SCS or surgery. There are currently no biologic treatments approved for CRSwNP in adolescents.

Lebrikizumab is being evaluated in this study (J2T-MC-KGBU), a pivotal Phase 3, multinational, multicenter, randomized, double-blind, placebo (PBO)-controlled, parallel group study to evaluate the efficacy and safety of lebrikizumab compared to PBO in participants with CRS with bilateral nasal polyps (NP) who receive background therapy with intranasal corticosteroids (INCS). This 72-week study will evaluate the efficacy of lebrikizumab in reducing the signs and symptoms of CRS with bilateral NP.

2.2 Background Information

2.2.1 Pathobiology and Clinical Manifestations of CRSwNP

CRSwNP is a chronic inflammatory condition associated with significant morbidity and is estimated to affect 1% to 4% of the general population and 25% to 30% of patients with CRS (Stevens et al 2016; Fokkens et al 2020). CRSwNP is much less common in the pediatric population (Fokkens et al 2020; Tan et al.2013). CRSwNP is characterized by the loss of the immune barrier and increased or chronic inflammation in nasal passages. These conditions create increased nasal congestion and polyp formation. IL-4 and IL-13 induce activation of M2-type macrophages, which contribute to the pathogenesis of CRSwNP by inducing fibrin deposition, edematous remodeling, and polyp formation (Maspero et al 2022). The exact cause of NP is unknown, but allergy, asthma, infection, and aspirin sensitivity have been associated with this complex refractory disease in adults (Stevens et al 2016).

Nasal congestion is a major symptom in CRSwNP caused directly by physical obstruction from NP but can also be caused by mucosal inflammation either by irritants (eg, smoke, exhaust, or perfume) or allergens. IL-13-triggered inflammation causes venous engorgement, increased nasal secretions, and tissue swelling, further leading to airflow impairment and nasal congestion (Naclerio et al 2010).

2.2.2 Treatment of CRSwNP

CRSwNP can lead to recurrent secondary bacterial infections needing multiple courses of systemic antibiotics, and resulting antibiotic resistance is not uncommon in this population (Rosenfeld et al 2015). The treatments of CRSwNP are predominantly SCS, INCS, and/or surgery. While these treatments do provide short-term relief, a recent meta-analysis reported that 18.6% of patients have more than 1 polyp removal surgery (Loftus et al 2020), and 35% of patients who underwent surgery for polyp removal had recurrence of NP at 6 months (DeConde et al 2017).

Currently, dupilumab, omalizumab, and mepolizumab have been approved for the treatment of CRSwNP in adults and despite these treatments a proportion of patients still require rescue with SCS or surgery. There are currently no biologics approved for the treatment of CRSwNP in adolescents.

2.2.3 Lebrikizumab

Lebrikizumab is an immunoglobulin (Ig)G4 monoclonal antibody with activity against IL-13. It binds IL-13 with high affinity and a slow off-rate, thereby selectively inhibiting IL-13 signaling (Okragly et al 2023). Blockade of the IL-13 cytokine via the 4Rα/IL-13Rα1 pathway inhibits downstream effects and may provide benefit in diseases such as CRS where IL-13 signaling is centrally involved (Okragly et al 2023) (Section 4.2).

Lebrikizumab has been extensively studied in atopic dermatitis (AD). In the completed Phase 2 studies, lebrikizumab demonstrated a favorable safety profile and clinically meaningful improvements in key clinical outcomes. The Phase 3 pivotal studies, using an induction dose of lebrikizumab 250 mg every 2 weeks (Q2W) for 16 weeks followed by maintenance treatment with lebrikizumab 250 mg Q2W and every 4 weeks (Q4W) after 16 weeks, showed that lebrikizumab is an efficacious treatment option for adults and adolescents with moderate-to-severe AD when used with or without standard-of-care topical corticosteroids in adult and adolescent participants (aged ≥12 years of age and weighing

≥40 kg) (Paller 2023; Szefler 2022). In addition to showing strong efficacy in the measures of Investigator's Global Assessment and Eczema Area and Severity Index, lebrikizumab also demonstrated efficacy in a range of patient-reported quality of life endpoints including itch severity and interference of itch with sleep. Data from the AD studies have been submitted to regulatory agencies and are under review as support of marketing authorization for the treatment of AD.

2.3 Benefit-Risk Assessment

2.3.1 Benefit Assessment

This protocol compares treatment with lebrikizumab to treatment with PBO in participants with CRSwNP on a background therapy with INCS. Beyond the provision of standard-of-care therapy and disease monitoring throughout the study for participants in both treatment groups, it is possible that participants randomized to receive lebrikizumab will achieve the benefit of treatment with an agent that demonstrated efficacy in AD, using a similar dosing regimen that demonstrated efficacy in the pivotal AD studies. Both CRSwNP and AD are type 2 inflammation-mediated diseases characterized by elevations of IL-13.

2.3.2 Risk Assessment

Since this protocol follows a similar dosing regimen used in the pivotal Phase 3 studies for the AD program in adults and adolescents, a similar safety profile is expected with the use of lebrikizumab for the treatment of CRSwNP compared with the safety profile previously established with the use of lebrikizumab in the AD program. The frequencies of the known adverse drug reactions for lebrikizumab in participants who were exposed to any dose of lebrikizumab during the AD clinical program were keratitis, injection site reactions, conjunctivitis, and herpes zoster.

Eosinophilia (>5000 cells/mm^3) was uncommonly observed in participants treated with lebrikizumab. In general, the eosinophilia was transient and did not result in discontinuation.

With 12 months of treatment, some participants treated with lebrikizumab 250 mg developed antidrug antibodies (ADA), most of which were neutralizing and of low titer. The presence of ADA did not appear to be associated with changes to the pharmacokinetics (PK), efficacy, or safety of lebrikizumab.

No systemic hypersensitivity reactions (including anaphylactic reactions) were reported following administration of lebrikizumab.

Although individual events of malignancies were reported in participants receiving lebrikizumab in the AD clinical program, an association with increased risk of malignancy has not been established.

No meaningful differences in the safety profile of lebrikizumab have been observed between adults and adolescents.

More detailed information about the known and possible benefits and risks and reasonably expected adverse events (AEs) of lebrikizumab may be found in the IB.

2.3.3 Overall Benefit-Risk Conclusion

Limitations on the current standards of care for CRSwNP demonstrate an unmet medical need. Based on CRSwNP and AD having a common pathophysiology and the current safety data from the AD clinical program, it is possible that participants with CRS with bilateral NP receiving lebrikizumab and background INCS following this protocol will achieve a similar benefit from participation, like participants in the AD program who were treated with lebrikizumab.

3 Study Objectives, Endpoints, and Estimands

3.1 Objectives and Endpoints

The objectives and endpoints are presented in Table 3-1. All objectives and endpoints in the table will be analyzed for the adult cohort of participants. All endpoints will also be collected in the adolescent cohort but will be summarized separately for that cohort using descriptive statistics and listings.

Table 3-1 Objectives and Endpoints

Objectives	Endpoints
Primary:	
• To evaluate the efficacy of lebrikizumab 250 mg Q2W compared to PBO in reducing nasal congestion severity and endoscopic NPS on background INCS at Week 24	• Mean CFBL at Week 24 in participant reported NCS severity • Mean CFBL at Week 24 in endoscopic NPS
Key Secondary:	
• To evaluate the efficacy of lebrikizumab in reducing the signs and symptoms in participants	• Mean CFBL at Week 56 in endoscopic NPS • Mean CFBL at Week 56 in participant reported NCS • Mean change in opacification of sinuses measured by the LMK from baseline to Weeks 24 and 56 • Mean change in FEV_1 from baseline to Weeks 24 in patients with asthma at baseline • Mean CFBL in severity of loss of smell at Weeks 4, 24, and 56 • Mean CFBL in postnasal drip at Weeks 24 and 56 • Proportion of and time-to-event for participants receiving systemic corticosteroids, and/or approved biologics for CRSwNP rescue use, and/or planned surgery of NP during study treatment period

Other Secondary:
• To compare the efficacy of lebrikizumab, compared to PBO, as measured by clinician assessments, and as assessed by PROs and quality of life measures in participants
	• Mean changes in the following from baseline by visit:
	  • Participant reported NCS severity
	  • Endoscopic NPS
	  • Opacification of sinuses measured by the LMK
	  • Severity of loss of smell as assessed by participant daily eDiary score
	  • Postnasal drip assessed by participant daily eDiary score
	  • FEV_1
	  • Severity of loss of taste as assessed by participant daily eDiary score
	  • Severity of facial pain/pressure as assessed

Objectives	Endpoints
	by participant daily eDiary score • Severity of rhinorrhea as assessed by participant daily eDiary score • Severity of CRS symptoms (visual analog scale) • 22-item Sino-nasal Outcome Test • University of Pennsylvania Smell Identification Test • Asthma Control Questionnaire-6 • Nasal peak inspiratory flow • EuroQol 5 Dimension 5 Level • WPAI+CIQ:CRSwNP • Patient Global Impression of Severity • PROMIS Anxiety Short Form v1.0 – Anxiety 8a • PROMIS Depression Short Form v1.0 – Depression 8a • Mean score for Patient Global Impression of Change
Exploratory: • To characterize the pharmacokinetics of lebrikizumab over the course of the study • To characterize immunogenicity and changes in exploratory biomarkers over the course of the study • To analyze genetic variation in relation to drug response	• Serum concentration of lebrikizumab at visits identified in the SoA (Table 1-1) • Immunogenicity (antidrug antibodies), total IgE, and nasal and blood biomarkers at visits identified in the SoA (Table 1-1) • Pharmacogenomic analysis
Safety: • To describe the safety and tolerability of lebrikizumab	• Incidence of AEs and SAEs; postbaseline values and changes over time of clinical laboratory evaluations, and vital signs

Note: Adolescent participants' efficacy and safety data will be summarized separately from that of the adult participants.

Abbreviations: AE = adverse event; CFBL = change from baseline; CRSwNP = chronic rhinosinusitis with nasal polyps eDiary = electronic diary; FEV_1 = forced expiratory volume in 1 second; IgE = immunoglobulin E; LMK = Lund Mackay score; NCS = nasal congestion score; NP = nasal polyps; NPS = nasal polyp score; PROs = patient-reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; Q2W = every 2 weeks; SAE = serious adverse event; SoA = Schedule of Activities; WPAI+CIQ:CRSwNA = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment: chronic rhinosinusitis with nasal polyps.

3.2 Estimand

The primary estimand is a hybrid estimand representing the primary clinical question of interest: what is the difference in means between treatment conditions (lebrikizumab versus PBO), in the target adult patient population, without NP surgery, change to another approved biologic therapy, or long-term use of SCS (greater use than the definition for short-term use below) or nasal saline lavage with corticosteroids (>10 days), and regardless of the study treatment discontinuation or short-term use of SCS?

The primary estimand is described by the following attributes:

A. Population: participants with CRS with bilateral NP.

B. Treatment: lebrikizumab versus PBO with background INCS.

C. Variable of interest: the primary and key secondary endpoints unless specified otherwise. Further details on the endpoints are provided in Table 3-1.

D. Population-level summary: difference in population means between lebrikizumab and PBO.

E. Handling of intercurrent events (ICEs).

- Treatment discontinuation: treatment policy strategy.
- Short-term use of SCS treatment: treatment policy strategy.
- NP surgery, change to another approved biologic therapy or long-term use of SCS or nasal saline lavage with corticosteroids: composite strategy.

Regarding to the co-primary endpoints, change from baseline (CFBL) in endoscopic nasal polyp score (NPS) and CFBL in nasal congestion score (NCS) severity using difference in population means will be compared between participants treated with lebrikizumab and PBO in combination with background standard-of-care, regardless of treatment discontinuation or short-term use of SCS treatment. Short-term use of SCS is defined as ≤1 mg/kg prednisone equivalent per day for ≤7 days of use. Nasal polyp surgery, change to another approved biologic therapy, or long-term use of SCS (greater use than the definition of short-term use above) or nasal saline lavage with corticosteroids will be considered as treatment failures.

Long-term use of nasal saline lavage with corticosteroids is defined as continuous use for >10 days. In the case of treatment failure, endoscopic NPS and NCS severity values will be replaced with the worst possible scores.

The primary estimand with rationale for the strategies to address ICEs is presented in Table 3-2.

Table 3-2 Description of Primary Estimand and Missing Data Imputation Methods

Estimand	Treatment Discontinuation	Rescue Therapy		Missing Data Imputation Method
		Short-term use of SCS Treatment	Nasal Polyp Surgery, Change to Another Approved Biologic Therapy or Long-term Use of SCS or Nasal Saline Lavage with Corticosteroids	
Primary Estimand	Treatment policy: As observed	Treatment policy: As observed	Composite: set to worst possible scores	Primary analysis: Multiple Imputation

Abbreviation: SCS = systemic corticosteroids.

4 Study Design

4.1 Overall Design

This is a Phase 3, multinational, multicenter, double-blind, PBO-controlled, parallel group, randomized clinical study to evaluate the efficacy and safety of lebrikizumab in approximately 510 adult participants (≥18 years of age) with CRS and bilateral NP who receive background therapy with INCS. Enrollment will also be open to adolescents at least 12 years of age and weighing at least 40 kg. Any adolescent participant enrolled will not contribute to the target number of 510 participants.

This study has 4 study periods:

- Screening (up to 30 days)
- Run-in (4 weeks)
- Randomized treatment (56 weeks), which includes an induction period (24 weeks; Week 0 to Week 24) and a maintenance period (32 weeks; Week 24 to Week 56)

- Safety follow-up (SFU; 8 weeks), starting after the study site visit at Week 56. For participants who complete the final maintenance visit at Week 56, SFU (Visit 801) will occur at Week 64 (12 weeks after the last dose scheduled at Week 52). If a participant withdraws from the study early, SFU (Visit 801) will be scheduled to occur 12 weeks after the last dose received.

The maximum planned duration of study participation for each participant will be up to approximately 72 weeks.

Adult participants meeting the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively) will be randomly assigned 1:1:1 to the following treatment arms at baseline (Visit 3) (see Table 6-2 and Table 6-3 for dosing details):

- Lebrikizumab Q2W/Q4W Arm: Lebrikizumab 500 mg loading dose at Week 0 and Week 2, followed by lebrikizumab 250 mg Q2W through Week 24 (induction period) and then lebrikizumab 250 mg Q4W through Week 56 (maintenance period).

- Lebrikizumab Q2W/Q8W Arm: Lebrikizumab 500 mg loading dose at Week 0 and Week 2, followed by lebrikizumab 250 mg Q2W through Week 24 (induction period) and then lebrikizumab 250 mg Q8W through Week 56 (maintenance period).

- PBO Arm: PBO Q2W through Week 24 (induction period) and then PBO Q4W through Week 56 (maintenance period).

Randomization for adult participants will use block randomization with fixed block size and will be stratified by the following factors:

- Asthma and/or aspirin-exacerbated respiratory disease (AERD) versus no asthma/no AERD

- Prior NP surgery versus no prior NP surgery

- Geographic region (North America, Europe, rest of the world)

Participants, investigators, and study site staff will be fully blinded to the treatment arm (Section 6.1 and Section 6.4).

Enrollment of adolescents will be open-label, with all eligible adolescents assigned to the lebrikizumab Q2W/Q4W dose regimen.

Study assessments and procedures will be conducted according to the Schedule of Activities (SoA; Table 1-1). In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the sponsor or the investigator, per local regulatory agency/ethics requirements (Appendix 15.6).

Intranasal mometasone furoate will be required as background intervention during the 4-week run-in period as well as throughout the randomized treatment period (Week 0 to Week 56). Participants may continue mometasone furoate during the SFU period at the discretion of the investigator.

4.2 Scientific Rationale for Study Design

Much of the scientific rationale for the study design was derived from the 2023 Food and Drug Administration (FDA) (DHHS 2023) guidance to industry that addresses developing drug products for treating CRSwNP, including the following:

- Sponsors should permit participants to use standard-of-care rescue therapies such as INCS sprays, antibiotics, SCS, and surgery (Section 6.10.2.2). Mometasone furoate is a globally available and approved treatment for CRSwNP.

- The United States (US) FDA recommends randomized, double-blind, PBO-controlled, parallel-group studies, preferably with a 2- to 4-week period before randomization to assess symptom severity or eligibility.

- The study duration and timing of efficacy assessments should be guided by the goals of therapy, mechanism of action of the drug and its expected onset of action, and the time frame in which a clinical benefit is expected to be observed. Because CRSwNP is a chronic disease, the FDA recommend studies of at least 24 weeks, but ideally 52 weeks, in duration. Sponsors should consider longer studies to determine potential safety concerns and the effect on efficacy outcomes such as reduction in SCS use, surgery, and recurrence of NP.

- The final treatment visit is planned for Week 56 to allow participants on lebrikizumab Q8W dosing to complete their final dosing interval for the end-of-treatment assessment.

- The randomized treatment period will be double-blind and PBO-controlled and is designed to minimize bias in the evaluation of the efficacy and safety of lebrikizumab, relative to PBO, through 56 weeks of treatment. Placebo is chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions. The use of PBO is considered appropriate, as Phase 3 studies with lebrikizumab have not been conducted to date in adults with CRSwNP. The participants assigned to PBO treatment will also be using mometasone furoate to minimize the burden on these participants. Thus, a PBO comparator is necessary to understand lebrikizumab's true safety and efficacy.

- In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

- Due to the very low prevalence of the disease in adolescents, no specified target number of adolescents is proposed, and all participants will be assigned to open-label lebrikizumab.

4.3 Justification for Dose

The dose regimen to be studied in CRSwNP is based on adult and adolescent lebrikizumab data from the AD and asthma programs. Since CRSwNP and AD are type 2 inflammation-mediated diseases characterized by elevations of IL-13, lebrikizumab is expected to have a consistent safety profile in CRSwNP. Data from studies of lebrikizumab adolescents weighing ≥40kg with AD and asthma indicate that efficacy and safety findings in adolescents are similar to those observed in adults (Paller 2023; Szefler 2022).

Loading and Induction Dose:

The loading and induction dosing regimen for lebrikizumab in this study is the same regimen that demonstrated efficacy and safety in the pivotal AD studies. The loading dose is designed

to achieve PK steady state as quickly as possible in order to accelerate disease control. This approach was shown to be successful in the AD studies.

Maintenance Doses:

Once clinical response has been achieved, the long half-life of lebrikizumab provides the ability to maintain the efficacy with a lower dosing frequency. This dosing scheme has been studied in the AD clinical program where efficacy effects were found to be durable and there was no discernable difference between the maintenance of efficacy using a Q2W or Q4W maintenance dose regimen. In addition, PK/PD modeling of the AD data suggested efficacy would be maintained with a lower dose frequency of Q8W, which is equivalent to a dose (125 mg Q4W) shown to be safe and effective in the asthma Phase 2 program.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

5 Study Population

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

The inclusion and exclusion criteria for enrolling participants in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria, the investigator should consult with the appropriate sponsor representative before enrolling the participant in the study.

5.1 Inclusion Criteria

Each participant must meet all of the following criteria to be enrolled in this study:

1. Adult participants ≥18 years of age at time of signing the informed consent form (ICF) and adolescent participants ≥12 to <18 years of age and weighing ≥ 40 kg at Visit 1. Legal age may vary depending on regulations of each country and country standards will be followed.

2. Physician-diagnosed CRS with bilateral NP.

3. Prior treatment with SCS for CRS or CRSwNP within the last 2 years (or a medical contraindication or intolerance to SCS), prior surgery for NP, or both.

4. Endoscopic bilateral NPS score of at least 5 out of 8, with a minimum score of 2 in each nasal cavity performed at screening (Visit 1) and baseline (Visit 3).

5. Ongoing symptoms for at least 8 weeks prior to study entry (screening [Visit 1]), including:

    a. Nasal congestion with moderate or severe symptom severity (score 2 or 3) at screening (Visit 1) (single day for Visit 1) and a weekly average severity score of at least 1 (range 0 to 3) at randomization (average of the 14 days prior to Visit 3 [baseline]), and

    b. At least one other symptom, such as, but not limited to, partial loss of smell (hyposmia), total loss of smell (anosmia), or anterior or posterior rhinorrhea.

6. Participants who have concomitant asthma must be stable in the 3 months prior to screening using permitted regular asthma treatment.

7. Participants must complete their eDiaries at least 4 out of 7 days every week in the 2 weeks prior to randomization visit (Visit 3 [baseline]).

8. Women of childbearing potential (WOCBP) must use at least 1 highly effective contraceptive or a combination of 2 effective contraceptive methods consistent with local regulations regarding the methods of contraception for those participating in clinical studies. WOCBP and women not of childbearing potential (WNOCBP) may participant in this study. See Appendix 15.1 for definitions and additional requirements related to contraception.

9. The adult participant or parent/legal guardian of an adolescent participant must understand the investigational nature of this study and sign an Institutional Ethics Committee (IEC)/Institutional Review Board (IRB)-approved written informed consent prior to receiving any study-related procedure. Adolescent participants must also understand the nature of the study and sign an informed assent document prior to receiving any study-related procedures as required by local regulations

10. Is willing and able to comply with all clinic visits, study-related procedures, and questionnaires, importantly including taking required background therapy and completing a daily electronic diary (eDiary).

5.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Has received a dose of lebrikizumab.
2. Is currently enrolled in any other clinical study involving an investigational drug, or any other type of medical research judged not to be scientifically or medically compatible with this study.
3. Has received treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to randomization.
4. Has a known hypersensitivity to any component of lebrikizumab or its excipients.
5. Has a contraindication or intolerance to mometasone furoate.
6. Leukotriene receptor antagonists within 4 weeks prior to screening (Visit 1).
7. Has received treatment with any rescue medication and/or has the need for surgery for NP (Section 6.10.3) during screening and/or run-in period.
8. Allergen immunotherapy (subcutaneous immunotherapy [SCIT]/sublingual immunotherapy [SLIT]) initiated within 6 months prior to screening, that is not on a stable dose (3 months prior to screening [Visit 1]) or may require a dose change during study.
9. Prior or current biologic treatment for CRSwNP and/or asthma and/or AD, including but not limited to omalizumab, dupilumab, mepolizumab, reslizumab, and benralizumab.
10. Has received treatment with any biologic or systemic immunosuppressants for inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory

bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis) prior to the baseline visit (Visit 3; randomization).

a. B cell-depleting biologics, including rituximab, within 6 months.

b. Other biologics within 5 half-lives (if known) or 8 weeks, whichever is longer.

c. Systemic immunosuppressants within 4 weeks prior to baseline (Visit 3).

11. Has had any sinus intranasal surgery (including nasal polypectomy) within 6 months prior to screening (Visit 1).

12. Has had prior sino-nasal surgery or sinus surgery changing lateral wall structure of the nose making it difficult to assess endoscopic NPS.

13. Has a history of severe asthma exacerbation in the previous year and documented use of SCS for asthma in the past 12 months.

14. Has a presence of any of the following conditions that may impact the assessment of endpoints at screening (Visit 1) or baseline (Visit 3):

    a. Nasal septal deviation occluding at least one nostril.

    b. Antrochoanal polyps.

    c. Acute sinusitis, acute nasal infection, or acute upper respiratory infection.

    d. Ongoing rhinitis medicamentosa.

    e. Presence of another diagnosis associated with NP (ie, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, Young's syndrome, primary ciliary dyskinesia, cystic fibrosis).

       Note: for adolescents, documentation for ruling out cystic fibrosis and primary ciliary dyskinesia is required.

    f. A nasal cavity tumor (malignant or benign).

    g. Evidence of fungal rhinosinusitis.

15. Has received any live or live attenuated vaccine (including Bacillus Calmette-Guerin vaccine or treatment) within 4 weeks prior to baseline (Visit 3), intends to receive a live attenuated vaccine (or Bacillus Calmette-Guerin treatment) during the study, or within 4 weeks after receiving the last dose of IP. Note: The following are not considered live vaccines: messenger RNA vaccines, vaccines with inactive viral elements, and/or non-replicating viral vector vaccines.

    Note: The investigator should assess if adolescent participant is up to date with immunizations following the local guidelines for vaccination prior to enrolling into the study. For adolescents who are under vaccinated, the investigator should document the benefit/risk rationale for enrolling the participants in the study.

16. Has a history of HIV infection or positive HIV serology.

17. Has a current infection or chronic infection with hepatitis B virus (HBV) (ie, positive for hepatitis B surface antigen [HBsAg] and/or polymerase chain reaction positive) (Section 8.3.7.6).

18. Has a current infection with hepatitis C virus (HCV) (positive for HCV RNA) (refer to Section 8.3.7.6).

19. Has a known liver cirrhosis and/or chronic hepatitis of any etiology.

20. Is diagnosed with active endoparasitic infections or at high risk of these infections.

21. Has a known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, in the opinion of the investigator.

22. Has had any of the following types of infection within 3 months prior to screening or develops any of these infections during screening or the run-in period:

    a. Serious (requiring hospitalization, and/or intravenous or equivalent oral antibiotic treatment).

    b. Opportunistic (as defined in Winthrop et al 2015, Appendix 15.3).

    c. Symptomatic herpes zoster infection not resolved at the time of screening. Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over).

    d. Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer), other than chronic rhinosinusitis.

    e. Recurring (including, but not limited to recurring cellulitis, chronic osteomyelitis). Note: Participants with only recurrent, mild, and uncomplicated orolabial and/or genital herpes may be permitted at medical monitor's discretion.

23. Has an active or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to baseline (Visit 3). Note: Participants may be rescreened after infections resolves (Section 5.3). A participant who has a vaginal candida infection or an oral candida infection and who is being treated only symptomatically and not requiring systemic anti-infectives may be considered for enrollment if other study eligibility criteria are met. Enrollment of participants with other uncomplicated local infections should be discussed with the sponsor's designated medical monitor.

24. Has a history of malignancy within 5 years prior to screening (exceptions include adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix).

25. Has any other medical or psychological condition that in the opinion of the investigator may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant because of their participation in this

clinical study, may make participant's participation unreliable, or may interfere with study assessments.

26. Has a severe concomitant illness(es) that in the opinion of the investigator would adversely affect participation in the study.

27. Has anosmia from COVID or any reason other than CRSwNP.

28. Participants who have a recent nose piercing that has not completely healed and could lead to nasal symptoms at the time of screening (Visit 1) or planning a new nose piercing during study participation.

29. Participants with forced expiratory volume in 1 second (FEV_1) 50% or less (of predicted normal) at screening (Visit 1).

30. In the opinion of the investigator, has clinically significant laboratory result abnormalities obtained at screening (Visit 1) or at (baseline [Visit 3]).

31. Female participant who is pregnant, breastfeeding, or is planning to become pregnant, or to breastfeed during the study.

32. Is a Lilly employee, family of a Lilly employee, or is an employee of any third party involved in the study who require exclusion of their employees.

33. Is an investigator site personnel directly affiliated with this study and/or their immediate families, where immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

34. Is a participant or caregiver unable or unwilling to make themselves available for the duration of the study, or is unwilling to follow study restrictions and procedures, including subcutaneous administration of study medication.

35. Has a history of chronic alcohol abuse, intravenous drug abuse, or other illicit drug abuse within the 2 years prior to screening.

36. Is otherwise unsuitable for inclusion in the study, in the opinion of the investigator.

5.3 Lifestyle Considerations

All study participants will be instructed not to donate blood or blood products or sperm or eggs during the study (including the run-in period) and for at least 18 weeks after the last dose of the IP.

Participants who are current smokers or who vape are not excluded.

5.4 Replacements and Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to the IP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory agencies. Minimal information includes demography, screen failure details, eligibility criteria, and any serious AEs (SAEs).

Individuals who are to be rescreened must first sign a new ICF, consent to the rescreening, and attest to their understanding of the study. Such individuals will be assigned a new participant number.

An individual may be rescreened only once. An individual who does not meet the criteria for participation in this study may be rescreened if the reason for screen failure has resolved and if the sponsor has approved the rescreening.

When a participant is rescreened, all the screening tests and procedures must be repeated. An additional chest x-ray is not needed, if the previous one has been done within 12 months from rescreening and the report is available.

6 Study Treatments

Study treatments intended to be administered in this study to all participants includes the IP (lebrikizumab and PBO) and mometasone furoate as a required background medication. The use of concomitant medications and rescue medications is described in Section 6.10.2 and Section 6.10.3, respectively.

6.1 Study Treatments Administered

This study involves administration of IP (lebrikizumab and or PBO) and background medication (mometasone furoate), as shown in Table 6-1.

Table 6-1 Study Treatments Administered

Study Treatment	Lebrikizumab	Placebo	Mometasone Furoate
Study Treatment Name	LY3650150	Placebo to match	INCS
Dose Formulation	PFS-NSD to deliver 2.0 mL	PFS-NSD to deliver 2.0 mL	Metered spray
Unit Dose Strength(s)	250 mg, 125 mg/mL	Matched PBO, lacking lebrikizumab	50 µg per spray
Dosage Level(s)	500 mg (2 PFS-NSD) loading dose	2 PFS-NSD loading dose	200 µg (2 sprays in each nostril), BID
	250 mg (1 PFS-NSD) induction and maintenance dose	1 PFS-NSD induction and maintenance dose	
Route of Administration	Subcutaneous injection	Subcutaneous injection	Nasal spray
Authorized as Defined by EU CTR	Not authorized	Not authorized	Authorized and used according to authorization

Note: Placebo study treatment is only applicable for adult participants.

Abbreviations: BID = twice daily; EU CTR = European Union Clinical Trials Register; INCS = intranasal corticosteroid; PBO = placebo; PFS-NSD = prefilled syringe with needle safety device.

The schedules for administration of blinded lebrikizumab Q2W/Q4W arm, lebrikizumab Q2W/Q8W arm, and PBO arm are presented in Table 6-2 and Table 6-3). Study sites will dispense study treatment for administration at home according to the SoA (Table 1-1). Study treatments will be supplied in accordance with current Good Manufacturing Practice. IP will be labeled as appropriate for country requirements.

Background medications will be dispensed to all participants for use throughout the study, according to the SoA (Table 1-1). Further details on dosing of background interventions are presented in Section 6.10.2.2. Participants who are not comfortable self-administering IP away from the study site may come to the study site for administration according to the "away" administration schedule. Refer to Section 4.1 for randomization and treatment assignments.

Table 6-2 Loading Dose and Induction Period Dosing Schedule

Week	W0 Clinic	W2 Clinic	W4 Clinic	W6 Clinic	W8 Clinic	W10 Away	W12 Away	W14 Away	W16 Clinic	W18 Away	W20 Away	W22 Away
Visit	V3	V4	V5	V6	V7	-	-	-	V8	-	-	-
Arm												
Lebrikizumab Q2W/Q4W	500 mg (2 injections)	500 mg (2 injections)	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Lebrikizumab Q2W/Q8W	500 mg (2 injections)	500 mg (2 injections)	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
PBO	2 PBO	2 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO

Abbreviations: PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; W = week (as in W0; Week 0).

Note: Participants who are not comfortable self-administering IP away from the study site may come to the clinic for administration according to the "away" administration schedule. Enrollment of adolescents will be open-label, with all adolescents assigned to the lebrikizumab Q2W/Q4W treatment arm.

Table 6-3 Maintenance Period Dosing Schedule

Week	W24 Clinic	W28 Away	W32 Away	W36 Away	W40 Clinic	W44 Away	W48 Away	W52 Away	W56 Clinic
Visit	**V9**	**-**	**-**	**-**	**V10**	**-**	**-**	**-**	**V11**
Arm									
Lebrikizumab Q2W/Q4W	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	No dose
Lebrikizumab Q2W/Q8W	250 mg	1 PBO	250 mg	1 PBO	250mg	1 PBO	250 mg	1 PBO	No dose
PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	1 PBO	No dose

Abbreviations: PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; W = week (as in W0; Week 0).

Note: Participants who are not comfortable self-administering IP away from the study site may come to the clinic for administration according to the "away" administration schedule. Enrollment of adolescents will be open-label, with all adolescents assigned to the lebrikizumab Q2W/Q4W treatment arm.

6.1.1 Instructions for Administration at the Study Site

The IP will be administered under medical supervision by the investigator or designee at scheduled study site (clinic) visits according to the SoA (Table 1-1), Table 6-2, Table 6-3, and instructions in the study reference manual. There must be at least 7 days between IP dosing. The dose of IP and study participant identification will be confirmed prior to dispensing IP. Study site staff may also administer the IP to participants who are not comfortable self-administering IP away from the study site and come to the study site for administration according to the “away” administration schedule.

Study sites will provide proper instruction on correct nasal spray technique for mometasone furoate.

6.1.2 Instructions for Administration Away From the Study Site

Study site staff will instruct participants in the administration of the IP and background intervention away from the study site according to Table 6-2 and Table 6-3 and instructions in the study reference manual. There must be at least 7 days between IP dosing. The participant or caregiver will be trained prior to beginning "away" injections and will be provided with instructions for use to take home. Participants will record away administration of the IP and background medication in an eDiary (Section 10.1.1).

Beginning at run-in and through Week 56, all participants will be required to use mometasone furoate 50 µg/actuation 2 sprays in each nostril twice daily (BID; total daily dose of 400 µg) (Section 6.10.2.2). Participants may continue on mometasone in the SFU period at the discretion of the investigator.

6.2 Preparation, Handling, Storage, and Accountability

The study reference manual provides general instructions for the handling and storage of the IP, as well as the study site’s responsibility and accountability for the administered products. For storage information for lebrikizumab and PBO, refer to the IP label.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IP received and that any discrepancies are reported and resolved before use of the IP.

Only participants enrolled in the study may receive study treatment and only personnel authorized by an investigator or by the sponsor may supply or administer study treatment.

All study treatment 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 site staff (unless the study treatment will be administered at home by the participant or caregiver). At home storage instructions are provided in the participants' instructions for use.

In addition, the investigator is responsible for keeping accurate records of when and how much IP is dispensed and used by each participant in the study. Only participants enrolled in the study may receive the IP and only authorized site staff may supply or administer the IP. Reasons for departure from the expected dispensing regimen must also be recorded in study source documents. At the completion of the study, to satisfy regulatory requirements regarding IP accountability, all IP will be reconciled and retained or destroyed according to applicable regulations.

Unused IP must not be discarded or used for any purpose other than for administration to participants enrolled in this clinical study. The IP that is dispensed to a participant, but not administered by the participant, must be returned to the study site for drug accountability.

Further guidance and information for the final disposition of unused IP are provided in the study reference manual.

The investigator has the responsibility for keeping accurate records of background medication (mometasone furoate) dispensed to participants and corresponding to recordkeeping responsibility.

The sponsor will be responsible for delivering IP to study sites.

6.3 Assignment to Investigational Product

All participants will be centrally assigned to IP using an interactive web response system (IWRS). Before the study is initiated, the log-in information and directions for using the IWRS will be provided to each study site.

Assignment for adult participants will be randomized and stratified by asthma and/or AERD versus no asthma/no AERD, prior NP surgery versus no prior NP surgery, and geographic region (North America, Europe, rest of the world). All eligible adolescents will be assigned to open-label lebrikizumab Q2W/Q4W treatment.

6.3.1 Other Supplies

An eDiary (Section 10.1.1) may be provided to each study site for each participant, and electronic tablets will be provided for capture of patient-reported outcome (PRO) data at study site visits.

The sponsor or the study site will supply background medication (mometasone furoate).

6.4 Blinding

This is a double-blind study for the adult cohort of participants. The sponsor or designee(s), the investigator, study site staff, and the participant will be blinded to treatment assignment. The integrity of the clinical study will be maintained by observing the treatment blind.

Adult participants assigned to the Q2W/Q8W lebrikizumab arm will receive PBO on alternate scheduled dosing days during the maintenance period to maintain blinding (Table 6-3). Adult participants assigned to the PBO arm will receive Q4W injections during the maintenance period (Table 6-3).

Adolescent participants will not be blinded to treatment as they will be assigned to open-label lebrikizumab Q2W/Q4W.

6.4.1 Breaking the Blind

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's IP assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify the sponsor or designee(s) within 24 hours. The date on which the code was broken together with the identity of the person responsible must also be documented.

If an investigator, study site staff performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician for the participant to continue in the study.

6.5 Compliance With Planned Study Treatment Administration

Details on administration of the study treatment in the study site are in Section 6.1.1. When participants are dosed at the study site, they will receive the study treatment directly from the investigator or designee under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and in the electronic case report form (eCRF). The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the site staff other than the person administering the study treatment.

Details on self-administration away from the study site are in Section 6.1.2. When participants self-administer study treatment away from the study site, compliance with study treatments will be assessed at each visit. Compliance will be assessed by review of the eDiary and counting of returned IP and will be documented in the source documents and in the eCRF. Deviation(s) from the prescribed dosage regimen should be recorded. The participants will record their dosing of study treatment (IP and background) in their eDiaries (Section 10.1.1).

A record of the study treatment dispensed to and administered by each participant or caregiver must be maintained and reconciled with study treatment and compliance records. A participant will be considered compliant with the IP dosing regimen if the participant receives 75% of the expected number of injections while enrolled in the study. Compliance with protocol-specified background medication will be required and monitored for each participant.

6.6 Dose Modification

Dose modifications of the IP are not allowed, except for background therapy as noted in Section 6.10.2.2 in this study. Details are specified in the study reference manual.

6.7 Continued Access to Investigational Product After the End of the Study

No continued access to IP is planned after the end of this study.

6.8 Management of Overdose

An overdose is any dose of IP given to a participant or taken by a participant, accidentally or intentionally, that exceeds the dose specified in the protocol. In case of suspected overdose, hematology, clinical chemistry, vital signs, and oxygen saturation should be monitored and supportive care provided as necessary.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately, and
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.

Whenever possible and considering the safety of the participant, decisions regarding dose interruptions should be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.9 Management of Medication Errors

Medication errors at a study site will be managed by the investigator or their designated qualified medical professional.

To help identify medication errors away from the study site, study site staff will provide instructions for correct use of IPs (including written instructions) and for reporting medication errors or by contacting the study site in case of emergency (eg, a nonparticipant uses an IP).

6.10 Prior, Concomitant, and Rescue Medications and Therapies

Any medication (including vaccines and over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is taking at the time of screening or subsequently during the study enrollment or receives during the study must be recorded, including the following:

- Identity (specific to product name if a combination drug product), spelled correctly.
- Reason for use.
- Dates of administration, including start and end dates.
- Dosage information, including dose, frequency, and route of administration.

The medical monitor should be contacted if there are any questions regarding prior or concomitant therapy.

6.10.1 Prior Medications

A history of prior medications and relevant therapies should be collected as part of the medical history taken at screening. Restrictions on prior medications and therapies are found in the exclusion criteria (Section 5.2).

6.10.2 Concomitant Medications

All medications (including vaccines and over-the-counter drugs or prescription medicines, herbal supplements, vitamins, and antacids) taken/used at screening and throughout the study must be recorded. The investigator is expected to examine the acceptability of all concomitant medications, topical preparations, and dietary supplements taken by the study participants.

The use of concomitant medications for other medical conditions (eg, hypertension, diabetes, acute infections) is permitted during this study (Section 6.10.2.2). Inhaled corticosteroids (ICS) and combination with long-acting bronchodilators to control asthma are permitted if on stable doses for 3 months prior to screening (Section 5.1).

Medication entries should be specific to product name (if a combination drug product) and spelled correctly.

Information on the dose, unit, frequency, route of administration, start date, discontinuation date, and indication will be recorded.

The use of any concomitant medication must relate to an AE listed on the AE page in the eCRF or the participant's medical history unless it is a supplement or used as preventive care.

6.10.2.1 Prohibited Concomitant Medications

In addition to the medications listed in Section 5.2, the following will be prohibited during the study:

- Daily aspirin for treatment of AERD (aspirin is allowed as needed for pain relief or other indications).
- Intranasal antihistamines or combination intranasal corticosteroid antihistamines (eg, azelastine, olopatadine/mometasone furoate).
- Any biologic not approved for CRSwNP according to local regulatory authorization.
- Systemic antimicrobials >10 days.
- Nasal saline lavage with antibiotics and/or nasal saline lavage with corticosteroids (>10 days).
- Any systemic immunosuppressive treatment.
- Allergy immunotherapy (SCIT/SLIT), except if initiated more than 6 months prior to screening (Visit 1) and the dose is stable 3 months prior to screening (Visit 1) with no change in dose during the study.
- Use of INCS (other than mometasone furoate).
- Long-term course (>7 days) of SCS for any indications.

- Use of SCS between screening (Visit 1) and baseline (Visit 3) (screening and run-in period).
- Fluticasone propionate.
- Oral decongestants for any length of time to treat CRSwNP or oral decongestants >5 days to treat an acute adverse event.
- Intranasal decongestants, except as single use for nasal endoscopy.
- Leukotriene receptor antagonists.
- Live or live attenuated vaccines.

Participants who take any prohibited medications must discontinue from IP, but can remain in the study, unless the investigator decides to withdraw the participants from the study.

6.10.2.2 Allowed Medications

Concomitant medications participants can take during the study are presented in Section 6.10.2. Participants will be allowed to use the following medications:

- INCS, mometasone furoate 50 µg/actuation 2 sprays in each nostril BID (total daily dose of 400 µg) required by all participants during run-in period and through Week 56, if participants are unable to tolerate BID dosing or a specific regulatory requirement preventing use of this dose, participants can stay on a lower dose of 200 µg mometasone furoate (2 sprays/nostril once a day). Use of mometasone furoate at a higher dose is not allowed.
- Stable dose of ICS (Section 6.10.2).
- Nasal saline lavage, except on the day of the visit.
- Nasal saline lavage with antibiotics and/or nasal saline lavage with corticosteroids (≤10 days), except on the day of the visit.
- Single topical decongestants and single topical anesthetic administered for the purpose of nasal endoscopy.

- Local anesthetics (for example, EMLA cream) consistent with local prescribing information are permitted during the study visit to ease discomfort associated with venipunctures.
- Systemic antimicrobials ≤10 days.
- Stable doses of ICS, short-acting beta agonist, ICS/long-acting beta2 agonists, and long-acting muscarinic antagonists.
- Systemic antihistamines.
- Oral decongestants ≤5 days used to treat any acute adverse event other than CRSwNP.
- Non-live vaccines.
- Stable dose allergy immunotherapy (SCIT/SLIT) initiated >6 months prior to screening (Visit 1).
- Stable dose methylxanthines (eg, theophylline, aminophyllines).
- Short-term course (≤7 days) of SCS for any indications (Section 6.10.3).

6.10.3 Rescue Medication and Surgery for CRSwNP

Investigators should conduct efficacy (PROs and endoscopy) and safety assessments before starting any rescue medication. An unscheduled visit should be used for this purpose if necessary.

During the induction and maintenance, if the participant experiences worsening signs and symptoms that require medical intervention based on clinical evaluation by the investigator, the investigator may consider the following rescue treatment.

- Nasal saline lavage with antibiotics and/or nasal saline lavage with corticosteroids.
- SCS.
- Approved biologic for CRSwNP based on local regulatory approval.
- Need for surgery for NP.

Participants who receive rescue medication or plan for NP surgery must comply with the following:

- Participants receiving nasal saline lavage with antibiotics and/or nasal saline lavage with corticosteroids (≤10 days) during the study will continue on IP, unless the investigator decides to discontinue IP.
- Participants receiving nasal saline lavage with antibiotics and/or nasal saline lavage with corticosteroids (>10 days) during the study will discontinue IP, but can remain in the study, unless the investigator decides to withdraw the participant from the study.
- Participants receiving short-term SCS (≤7 days) rescue treatment during the study will continue on IP unless the investigator decides to discontinue IP.
- Participants receiving long-term SCS (>7 days) rescue treatment during the study will discontinue IP, but can remain in the study, unless the investigator decides to withdraw the participants from the study.
- Participants who receive an approved biologic for CRSwNP as a rescue treatment will discontinue IP but can remain in the study, unless the investigator decides to withdraw the participant from the study.
- Participants who need surgery for NP as a rescue treatment will discontinue IP, but can remain in the study, unless the investigator decides to withdraw the participant from the study. These participants may continue IP until the date of surgery.

7 Discontinuation From Investigational Product and Participant Withdrawal from the Study

7.1 Discontinuation of Investigational Product

Participants may discontinue from the IP at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep participants in the study. Participants may continue the study even if discontinuing IP.

The reasons for participants discontinuing the IP, based on the judgment of the investigator and/or the sponsor, will be recorded. At the discretion of the investigator, a participant may be discontinued from the IP for any of the following reasons:

- The participant discontinues IP for any reason, including the following:
  - Does not tolerate the IP
  - Does not perceive a benefit from the IP
  - Prefers an alternative treatment
  - Other reason (to be specified in the eCRF)
- The participant experiences a serious or intolerable AE(s) that in the investigator's opinion required discontinuation from IP.
- The participant has laboratory safety results that revealed clinically significant hematologic or biochemical changes from the baseline values.
- In the opinion of the investigator, the participant should permanently discontinue the IP for safety reasons.
- The participant develops of any new medical condition or contraindication that would render continued administration of the IP unsafe in the investigator's opinion.
- The participant has an intercurrent illness that would, in the opinion of the investigator, affect assessments of clinical status to a significant degree.

- Other reasons (to be specified in the eCRF).

- Participants who take any prohibited concomitant medication or rescue intervention listed in Section 6.10.2.1 and Section 6.10.3 must discontinue IP but can continue in the study.

7.1.1 Liver Chemistry Stopping Criteria

Refer to Section 8.3.7.7 for hepatic criteria for IP interruption or discontinuation.

Discontinuation of IP because of clinically significant abnormal liver test results should be considered by the investigator in consultation with the medical monitor when a participant meets one of the conditions presented in Section 7.1, or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.2 Temporary Interruption of Investigational Product

Some possible reasons for temporarily withholding the IP include, but are not limited to:

- Serious or opportunistic infections (Section 5.2 and Appendix 15.3). The IP is to be withheld until resolution of all acute clinical signs and symptoms, and completion of all appropriate anti-infective treatment.

- HBV DNA results are reported as positive, or as detecting HBV DNA, but HBV DNA is below the level of quantification. The sponsor's designated medical monitor should be contacted regarding study status of the participant. HBV DNA testing is to be repeated as soon as is feasible. If HBV DNA is confirmed as positive, the participant must be permanently discontinued from IP (Section 7.2.1).

- Hepatic event abnormalities are presented in Section 8.3.7.6.

- Liver test abnormalities are presented in Section 8.3.7.7.

7.2 Withdrawal From the Study

Participants may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. The investigator should discontinue a participant from the study if they think that continuation would be detrimental to the participant's well-being.

The investigator must withdraw a participant from the study if the participant is known to be pregnant.

Withdrawal from the study is expected to be uncommon. If the participant is unwilling or unable to remain in the study, the participant will complete procedures for an early discontinuation (termination) visit and posttreatment follow-up, if applicable.

Refer to the SoA (Table 1-1) for data to be collected at the time of discontinuation of the IP and follow-up and for any further evaluations that need to be completed.

The reasons for participants withdrawing from the study, based on the judgment of the investigator and/or the sponsor, will be recorded. At the discretion of the investigator, a participant may withdraw from the study for any of the following reasons:

Investigator Decision

1. The investigator decides that the participant should be withdrawn from the study. Some examples may include:
    - Intercurrent illness that would, in the opinion of the investigator, affect assessments of clinical status to a significant degree;
    - Treatment-related AEs that are clinically significant, deemed persistent, in the opinion of the investigator;
    - Unacceptable toxicity occurred; or
    - The investigator or sponsor decided to withdraw their participation in the study.

Participant Decision

1. The participant was unwilling or unable to comply with the protocol.
2. The participant enrolled into another interventional clinical study in which an

investigational treatment or approved therapy for investigational use is administered.

3. The participant was lost to follow-up.
4. The participant withdrew consent.

Although a participant is not obliged to give their reason(s) for withdrawal from the study, the investigator should make every effort to ascertain the reason(s) while fully respecting the participant's rights.

7.2.1 Mandatory Withdrawal From the Study

The following are findings requiring permanent discontinuation and withdrawal from the study if a participant develops any of the following conditions during the study:

- Malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- Serious or opportunistic infection that in the opinion of the investigator merits the study treatment being discontinued. Such infections may include, but are not limited to:
  - HIV/AIDS infection
  - Active TB infection or untreated latent TB infection
  - HCV RNA positive
  - HBV DNA positive: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification. The participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study treatment. Timing of discontinuation from study treatment relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard-of-care.

7.2.2 Withdrawal of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant must be discontinued from the study unless there are circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor-designated medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor-designated medical monitor to allow the inadvertently enrolled participant to continue in the study.

7.3 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 study site for a required study visit:

- The study 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 and ascertain whether the participant wishes to and/or should continue in the study.
- 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, 2 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.

If the participant continues to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

It is recommended that assessments/procedures completed at study site visits be performed in the following order as applicable:

1. Collection of AEs, concomitant medication

2. Measurement of vital signs and weight
3. PRO completion
4. Nasal peak inspiratory flow (NPIF) and spirometry
5. Endoscopy (NPIF and spirometry should be performed prior to endoscopy)
6. Laboratory sample collection – blood and urine
7. IP administration

Study assessments and procedures and their timing are summarized in the SoA (Table 1-1). Protocol waivers or exemptions from assessments or procedures are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the sponsor or the investigator, per local regulatory agency/ethics requirements (Appendix 15.6).

Repeat or unscheduled laboratory samples may be obtained for safety reasons or for technical issues with the samples.

8.1 Administrative, Screening, and Baseline Procedures and Assessments

Adherence to the study design requirements, including those specified in the SoA (Table 1-1), 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 screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1.1 Informed Consent and Assent Procedure

The procedural requirements of the informed consent and assent are described in Section 11.3.

8.1.2 Demographics, Medical History, and Prior Medication Procedure

Demographic information to be obtained will include age, sex, race, and ethnicity as described by the participant, and substance use history. The scientific rationale for this collection is the need to assess variable response in safety and/or efficacy based on race or ethnicity. Substance use history will also be collected. Only if all relevant data are collected can this assessment be made.

Medical history to be obtained will include determining whether the participant has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing the ICF. Ongoing conditions are considered concurrent medical conditions.

Medication history (ie, prior medications) to be obtained includes any medication relevant to eligibility criteria and safety evaluation stopped at or within the specified period of time prior to screening (Visit 1).

Physical examination (including height) is described in Section 8.3.3 and Section 8.3.4.

Assessment of vital signs (including weight) is described in Section 8.3.5.

8.2 Efficacy Assessments

Each participant's CRSwNP will be assessed as specified in the SoA (Table 1-1).

Electronic clinical outcome assessments (eCOAs) will be completed by participants using an eDiary and an on-site tablet (Table 1-1 and Section 10.1.1). The eDiary will be completed by participants around the same time each day (preferably in the morning) starting from run-in (Visit 2), and participants will be asked to record the severity of their nasal congestion, loss of smell, postnasal drip, loss of taste, facial pain/pressure, and rhinorrhea at its worst for the previous 24 hours using their eDiaries (Section 8.2.1, Section 8.2.5, Section 8.2.6, and Section 8.2.8). Adolescent participants should enter their responses into the ePRO devices (eDiary and tablet) independently but may have parental supervision if needed.

8.2.1 NCS Severity

NCS severity is rated by study participants using a 4-point scale (range from 0 to 3), where 0 corresponds to no symptoms and 3 corresponds to severe symptoms, and is collected on an eDiary (Table 1-1 and Section 10.1.1). Study participants are asked to record their nasal

congestion symptom severity, at its worst, for the previous 24 hours using a daily eDiary around the same time each day (preferably in the morning). The NCS at each assessed time point will be the average score over the previous 14 days. Participants are required to complete at least 4/7 days in each of the 2 weeks preceding randomization.

8.2.2 Endoscopic NPS

The endoscopic NPS is assessed by a centralized, blinded, independent review of nasal endoscopy video recordings. The total score is the sum of the right and left nasal cavity scores.

An otolaryngologist or allergist with clinical study experience, certified to perform nasal endoscopy, and access to spirometry with interpretation or an allergist who can identify an otolaryngologist as a sub-I for nasal endoscopy to perform the NPS evaluation.

For each nasal cavity, endoscopic NPS is graded based on polyp size from 0 to 4, where 0 = no polyps and 4 = large polyps (DHHS 2023). Endoscopic NPS will be calculated as the average of scores from 2 trained physician assessors reviewing video recordings of nasal endoscopies where assessors are blinded to participants' IP assignment. An adjudication process will be in place for discordant results between the 2 assessors. Additional details will be provided to the study sites.

Screening (Visit 1) endoscopy central reading will be available to the study site to confirm eligibility. At baseline (Visit 3), the nasal endoscopy will be performed to confirm eligibility with a local reading. The results from the central reading of the baseline (Visit 3) endoscopy will not be available at the time of randomization.

For the efficacy analysis, central reading for nasal endoscopy will be used.

8.2.3 Opacification of Sinuses

Central read on sinus computed tomography (CT) scans for the Lund Mackay score (LMK) will be performed. The CT scan should be performed at the time points listed in the SoA (Table 1-1).

In countries for which a specific approval procedure for the CT scan is required by a different committee than the local IRB/IEC, participants may be enrolled using a CT scan performed

in the previous year or perform an MRI of the sinuses between Visit 1 and Visit 2. These countries will be exempted from all the planned study CT scans until approval from these committees is received.

Review of the CT scans of the right and left frontal sinuses will include the use of a scoring system. The LMK scoring system is a 3-point grading scale where 0 = normal, 1 = partial opacification, and 2 = total opacification. The total score is the sum of the scores from each side and ranges from 0 to 24, where 0 indicates no disease and 24 indicates the most severe disease (Lund and Kennedy 1997).

The LMK scoring system rates each side separately (right/left) for each sinus:

- Frontal
- Maxillary
- Sphenoid
- Ostiomeatal complex
- Anterior ethmoid
- Posterior ethmoid

8.2.4 Spirometry

Spirometry is used to measure the physiologic air flow during FEV_1.

Spirometry will be performed in all participants at screening (Visit 1) after withholding the last dose of short-acting bronchodilator for at least 6 hours, using a study-supplied spirometer that meets the American Thoracic Society/European Respiratory Society recommendations. At subsequent visits, spirometry will be performed for only participants with asthma according to the SoA (Table 1-1). Normal FEV_1 values are typically ≥80% (Barriero and Perillo 2004). Lower FEV_1 values can indicate more severe asthma or other causes of airway restriction or obstruction. Spirometry will be conducted by trained and qualified personnel, according to procedures specified in the study reference manual.

8.2.5 Severity of Loss of Smell

Participant reported loss of smell has been identified through qualitative interviews with individuals with CRS as an important and bothersome symptom (Hall et al 2020; O'Quinn et al 2022) and is recommended as a secondary endpoint in the FDA Guidance (DHHS 2023). Loss of smell is rated by study participants using a 4-point scale, where 0 corresponds to no symptoms and 3 corresponds to severe symptoms. Study participants are asked to record the severity of their loss of smell, at its worst, for the previous 24 hours.

Loss of smell severity is collected on an eDiary (Section 10.1.1).

8.2.6 Postnasal Drip Score

Postnasal drip is rated by study participants using a 4-point scale, where 0 corresponds to no symptoms and 3 corresponds to severe symptoms. Study participants are asked to record the severity of their postnasal drip, at its worst, for the previous 24 hours. This assessment will be collected in the participant eDiary (Table 1-1 and Section 10.1.1).

8.2.7 Proportion of and Time-to-Event for Participants Receiving Systemic Corticosteroids, Approved Biologics for CRSwNP Rescue Use, and/or Planned Surgery of NP During Study Treatment

SCS Rescue

Systemic corticosteroids for rescue treatment of NP, or for another reason, will be prescribed to the participant by the site depending on local legislation/regulation, as needed. PROs and a nasal endoscopy should be performed before starting treatment with SCS. The investigator (or designee) records the date and dosing information on the appropriate page(s) in the eCRF. Indication for SCS use will be captured as the associated AE or medical history.

Approved Biologics

Approved biologics for CRSwNP for rescue treatment or for another reason will be prescribed to the participant by the site depending on local legislation/regulation, as needed. PROs and a nasal endoscopy should be performed before starting treatment with an approved biologic. The investigator (or designee) records the date and dosing information (daily dose,

duration, international nonproprietary name) on the appropriate page(s) in the eCRF. Indication for biologics use will be also captured as the associated AE or medical history.

Surgery (Actual or Planned) for NP

For participants who undergo or are planned for sino-nasal surgery for NP, the date of the decision for surgery and the surgery date (if available) will be recorded. PROs and endoscopy will be performed prior to surgery rescue. Surgery data will be collected through the participant's SFU visit.

8.2.8 Severity of Loss of Taste, Facial Pain/Pressure, and Rhinorrhea

Loss of taste, facial pain/pressure, and rhinorrhea are rated by study participants using a 4-point scale, where 0 corresponds to no symptoms and 3 corresponds to severe symptoms. Study participants are asked to record the severity of their loss of taste, facial pain/pressure, and rhinorrhea at its worst for the previous 24 hours using an eDiary. The loss of taste, facial pain/pressure, and rhinorrhea severity scores at each assessed time point will be the average score over the previous 14 days.

Loss of taste, facial pain/pressure, rhinorrhea are collected in the eDiary (Table 1-1 and Section 10.1.1).

8.2.9 Severity of Chronic Rhinosinusitis (VAS)

The visual analog scale (VAS) for CRS evaluates the total disease severity, and collected on a tablet at the study site (Table 1-1 and Section 10.1.1). Participants are asked to indicate on a 10 cm Chronic Rhinosinusitis Symptoms VAS the answer to the following question, “Over the past 7 days, how troublesome have your chronic rhinosinusitis symptoms been?” where 0 corresponds to "not at all troublesome" and 10 corresponds to "worst thinkable troublesome". The CRS VAS will be assessed at select study visits. Thresholds for disease severity have been defined as mild = 0 – 3, moderate = >3 – 7, and severe = >7 – 10 (Fokkens et al 2020).

8.2.10 Sino-Nasal Outcome Test (SNOT-22)

The 22-item Sino-nasal outcome test (SNOT-22) is a validated participant reported questionnaire that assesses the impact on health-related quality of life, and will be collected on a tablet at the study site (Table 1-1 and Section 10.1.1). It consists of 22 questions assessing sino-nasal and auricular function, psychological impact, productivity, and sleep

quality. Participants will be asked to recall their experiences over the past 2 weeks and rate their symptoms on a scale ranging from 0, which corresponds to no problem, to 5, which corresponds to problem as bad as it can be. The scores of the individual questions will be summed to create a total score that ranges from 0, which corresponds to no disease, to 110, which corresponds to worst disease. Lower scores indicate less impact. A change in a score of 8.9 points has been identified as the minimal clinically important difference (Hopkins et al 2009).

8.2.11 University of Pennsylvania Smell Identification Test (UPSIT)

The University of Pennsylvania Smell Identification Test (UPSIT) is a participant reported assessment of olfactory function which uses a "scratch and sniff" test of 10 odorants. Scores range from 0 – 40 with <18 equivalent to anosmia (complete loss of smell), 19 – 25 = severe microsmia, 26 – 30 = moderate microsmia, 31 – 34 mild microsmia, and 35 – 40 normosmia (normal smell appreciation) (Doty et al 1984; Doty 2015).

8.2.12 Asthma Control Questionnaire-6 (ACQ-6)

Asthma Control Questionnaire-6 (ACQ-6) is a 6-question validated participant reported questionnaire that assess the most common asthma symptoms, and is collected on a tablet at the study site only for participants with asthma (Table 1-1 and Section 10.1.1). The questions include:

- Woken by asthma;
- Symptoms on waking;
- Activity limitation;
- Shortness of breath;
- Wheezing; and
- Puffs/inhalation use.

Participants with a history of asthma will be asked to recall how their asthma had been during the previous week and to respond to the questions on a 7-point scale where 0 corresponds to no impairment and 6 corresponds to maximum impairment. An ACQ-6 score will be

calculated from the mean of the scores and expressed as a total control value out of 6, where 0 corresponds to totally controlled asthma and 6 corresponds to severely uncontrolled asthma. A minimal clinically important difference value for the ACQ-6 has been defined as a 0.5-point change (Juniper 1999, Juniper 2005).

8.2.13 Nasal Peak Inspiratory Flow

NPIF measures the maximum inspiratory flow rate through both nostrils during inspiration with results expressed in L/min. Participants with NPIF results >120 L/min represents no nasal obstruction (Mo et al 2021). NPIF will be performed according to the SoA (Table 1-1), using the highest of 3 readings. Measurement of NPIF will be conducted by trained and qualified personnel, according to procedures specified in the study reference manual.

8.2.14 EuroQol 5-Dimension 5-Level

The EuroQol 5-Dimension 5-Level (EQ-5D-5L) is a generic questionnaire that assesses health status, and is collected on a tablet at the study site (refer to Table 1-1 and Section 10.1.1). It includes a descriptive system comprised of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with each dimension having 5 levels. The questionnaire also includes a VAS where the respondent self-rates their health on a vertical VAS, with endpoints of "the best health you can imagine" and "the worst health you can imagine" (EuroQoL Group 1990; Herdman et al 2011; Remenschneider et al 2015).

8.2.15 Work Productivity and Activity Impairment plus Classroom Impairment Questions:CRSwNP (WPAI+CIQ:CRSwNP)

The Work Productivity and Activity Impairment plus Classroom Impairment Questions: chronic rhinosinusitis with nasal polyps (WPAI+CIQ:CRSwNP) is a patient-reported instrument used to assess impairments in work, classroom, and regular activities in patients with CRSwNP; it is also collected on a tablet at the study site (Table 1-1 and Section 10.1.1). It contains 10 items that measure the following:

- Employment status;
- Hours missed from work due to CRSwNP;

- Hours missed from work for other reasons;
- Hours actually worked;
- Degree CRSwNP affected productivity while working;
- Status of attending classes in an academic setting;
- Hours missed from class due to CRSwNP;
- Hours attended school/class;
- Degree CRSwNP affected productivity in classroom setting;
- Degree CRSwNP affected regular daily activities;

The WPAI+CIS:CRSwNP yields 4 subscores:

- Absenteeism (work or classroom time missed);
- Presenteeism (impairment at work or classroom/reduced on-the-job effectiveness);
- Work productivity loss (overall work or classroom impairment/absenteeism plus presenteeism); and
- Activity impairment.

Scores are calculated as impairment percentages (Reilly et al 1993), with higher numbers indicating greater impairment and less productivity, ie, worse outcomes.

8.2.16 Patient-Reported Outcomes Measurement Information System Scales

8.2.16.1 PROMIS Short Form v1.0 – Anxiety 8a

The Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety Short Form can be used with the general population and with individuals living with chronic conditions. The PROMIS Anxiety item bank assesses self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic

symptoms related to arousal (racing hear, dizziness). The PROMIS Anxiety Short Form 8a (v1.0) includes 8 questions which assess participants' symptoms over the previous 7 days. Response options range from 1=Never; 2=Rarely; 3=Sometimes; 4=Often; 5=Always. Total raw scores are converted to T-Scores with higher scores representing greater anxiety (PROMIS [healthmeasures.net]).

This assessment will be conducted according to the SoA (Table 1-1) and is collected on a tablet at the study site (Section 10.1.1).

8.2.16.2 PROMIS Short Form v1.0 – Depression 8a

The PROMIS Depression Short Form can be used with the general population and with individuals living with chronic conditions. The PROMIS Depression item bank assesses self-reported negative mood (sadness, guilt), views on self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). The PROMIS Depression Short Form 8a (v1.0) includes 8 questions which assess participants' symptoms over the previous 7 days. Response options range from 1=Never; 2=Rarely; 3=Sometimes; 4=Often; 5=Always. Total raw scores are converted to T-Scores with higher scores representing greater depression (PROMIS [healthmeasures.net]).

This assessment will be conducted according to the SoA (Table 1-1) and is collected on a tablet at the study site (Section 10.1.1).

8.2.17 Patient Global Impression of Severity/Patient Global Impression of Change

Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) scales will be collected to facilitate the assessment of clinically meaningful within-participant change for nasal congestion, loss of smell, and postnasal drip. The PGI-S and PGI-C will be collected on a tablet at the study site per the SoA (Table 1-1 and Section 10.1.1).

The PGI-S: nasal congestion asks the participant to rate the overall severity of their nasal congestion due to chronic rhinosinusitis over the past 14 days with response options of: no symptoms, mild, moderate, severe, and very severe.

The PGI-S: loss of smell asks the participant to rate the overall severity of their loss of smell due to chronic rhinosinusitis over the past 14 days with response options of: no symptoms, mild, moderate, severe, and very severe.

The PGI-S: postnasal drip asks the participant to rate the overall severity of their postnasal drip due to chronic rhinosinusitis over the past 14 days with response options of: no symptoms, mild, moderate, severe, and very severe.

The PGI-C: nasal congestion asks the participant to describe the overall change in their nasal congestion due to chronic rhinosinusitis since they started taking the new medication with response options of very much better, much better, a little better, no change, a little worse, much worse, and very much worse.

The PGI-C: loss of smell asks the participant to describe the overall change in their loss of smell due to chronic rhinosinusitis since they started taking the new medication with response options of very much better, much better, a little better, no change, a little worse, much worse, and very much worse.

The PGI-C: postnasal drip asks the participant to describe the overall change in their postnasal drip due to chronic rhinosinusitis since they started taking the new medication with response options of very much better, much better, a little better, no change, a little worse, much worse, and very much worse.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1-1).

8.3.1 Adverse Events

8.3.1.1 Definitions

8.3.1.1.1 AEs

The investigator, or qualified designee, is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study treatment or their clinical significance.

An AE is defined as any untoward medical occurrence in a participant enrolled into this study, regardless of its causal relationship to the study treatment. Participants will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to the IP or any event already present that worsens in either intensity after exposure to the IP.

Anticipated day-to-day fluctuations of preexisting diseases or conditions present or detected at the start of the study that do not worsen would not be considered AEs. Laboratory results of disease/disorders being studied and medical/surgical procedures are not AEs but rather the condition/event that leads to it is defined as an AE. Medication error, misuse, or abuse of IP, including any signs, symptoms, or clinical sequelae, are considered AEs.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AEs of special interest (AESIs), as defined in Section 8.3.1.1.2 and Section 8.3.1.1.5, respectively, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (Section 7.3). For product complaints (Section 8.3.1.1.3), the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the AE.

8.3.1.1.2 Serious Adverse Events

An SAE is defined as any event that:

- Results in death;
- Is immediately life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.1.1.3 Product Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of an IP. When the ability to use the IP safely is impacted, the following are also product complaints:

- Deficiencies in labeling information, and
- Use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to the IP used in clinical studies are collected to ensure the safety of participants, monitor quality, and facilitate process and product improvements.

Investigators will instruct participants to contact the study site as soon as possible if he or she has a product complaint or problem with the IP so that the situation can be assessed.

An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

Product complaints on product that is procured and supplied by the investigator, for example background intervention or rescue medication, will be reported per marketed label and in compliance with investigator's local procedures.

Product complaints will be reported by the investigator to the sponsor per instructions provided on the study-specific Product Complaint Form within 24 hours if a product complaint resulted in a serious event. If no SAE is related to a product complaint, then the investigator must report the product complaint within one business day.

8.3.1.1.4 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as a serious adverse reaction, for which the nature or severity is not consistent with the applicable product information (eg, IB for an unapproved investigational medicinal product). Reporting of SUSARs is presented in Section 8.3.1.3.2.

8.3.1.1.5 Adverse Event of Special Interest

An AESI (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor or designee are appropriate (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] E2F; Council for International Organization of Medical Sciences VI).

The AESIs for this study include:

- Conjunctivitis;
- Herpes infection (including herpes zoster); and
- Parasitic infection or an infection-related to an intracellular pathogen.

If an AESI is reported, the study site will be prompted to collect additional data and record it in the eCRF.

8.3.1.2 Eliciting and Documenting Adverse Events

AEs will be assessed from the time the participant signs the ICF and up until participation in the study has ended.

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All SAEs that occur during the study through the end of the follow-up period must be reported, even if not related to study treatment.

At every study visit, participants will be asked a standard nonleading question to elicit any medically-related changes in their well-being. Investigators and study site staff will take care to avoid introducing bias when detecting events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about event occurrences.

In addition to participant observations, AEs identified from any study data (eg, laboratory values, physical examination findings) or identified from review of other documents (eg, participant diaries) that are relevant to participant safety will be documented on the AE page in the eCRF.

8.3.1.2.1 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: These events require minimal or no treatment and do not interfere with the participant's daily activities.
OR

An event usually transient in nature and generally not interfering with normal activities.

Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning. Usually alleviated with additional specific therapeutic intervention.
OR

An AE that is sufficiently discomforting to interfere with normal activities.

Severe: These events interrupt a participant's usual daily activity and may require intensive therapeutic intervention. Severe events are usually incapacitating.
OR

An AE that is incapacitating and prevents normal activities.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious", which is based on participant/event outcome or action criteria associated with events that pose a threat to a participant's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

Changes in the severity/intensity of an AE should be documented to allow an assessment of the duration of the event at each grade of severity/intensity. AEs characterized as intermittent do not require documentation of onset or duration of each episode.

8.3.1.2.2 Assessment of Causality

The investigator must assess the relationship between the study treatment and the occurrence of each unsolicited AE (including SAEs) using clinical judgment. Where several different study treatments are administered, the investigator should specify, when possible, if the unsolicited AE could be causally related to a specific study treatment. When a causal relationship to a specific study treatment cannot be determined, the investigator should indicate that the unsolicited AE is related to all study treatments.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. The investigator will also consult the IB and/or

Summary of Product Characteristics and/or Prescribing Information for marketed products to assist in making their assessment.

Causality should be assessed by the investigator using the following question, and the answer recorded in the eCRF: Is there a reasonable possibility that the unsolicited AE may have been caused by the study treatment?

YES: There is a reasonable possibility that the study treatment contributed to the AE.

NO: There is no reasonable possibility that the AE is causally related to the administration of the study treatment. There are other, more likely causes and administration of the study treatment is not suspected to have contributed to the AE.

If an event meets the criteria to be determined an SAE (Section 8.3.1.1.2), additional examinations/tests will be performed by the investigator to determine **all** possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol-required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the IP, if applicable.
- An error in IP administration.
- Other cause (specify).

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to the sponsor.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change their opinion of causality after receiving additional information and update the SAE information accordingly.

The investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

8.3.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF.

The AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE. However, if the medical condition deteriorates at any time during the study, it should be recorded as an AE.

8.3.1.3.1 Reporting Serious Adverse Events

Any AE that meets the SAE criteria (Section 8.3.1.1.2) must be reported to Lilly immediately (ie, within 24 hours) after study site staff first learn of the event. If an SAE is determined to be related to study procedure(s) occurring at a study site visit before administration of the study treatment, the SAE will be reported before administration of the study treatment. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.

The sponsor has a legal responsibility to notify both the local regulatory agency and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information from the sponsor will review and then file it as appropriate and will notify the IRB/IEC, if appropriate according to local requirements.

If a participant dies during participation in the study or during the recognized SFU period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

8.3.1.3.2 Reporting Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all SUSARs and nonserious AESIs against cumulative study treatment experience to identify and expeditiously communicate possible safety findings to investigators, IRBs/IECs, and applicable regulatory agencies based on applicable legislation.

The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to EU regulatory requirements. The sponsor will comply with applicable regulatory requirements relating to safety reporting to the regulatory authority, per European Union Clinical Trial Regulation 536/2014 submission of SUSARs to the EudraVigilance database.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

To determine reporting requirements for single AE cases, the sponsor will assess the expectedness of these events using the reference safety information in the lebrikizumab IB or any available label for lebrikizumab at the time.

The sponsor will compare the severity of each SUSAR 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.

8.3.1.4 Follow-Up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, the event is considered to be stable, or the participant is lost to follow-up. For product complaints (Section 8.3.1.1.3), the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the AE.

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 or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The investigator will record new or updated information in the original completed eCRF and will submit any updated SAE data to sponsor, or designee, within 24 hours of receipt of the information.

8.3.2 Clinical Safety Laboratory Assessments

Refer to Appendix 15.4 for the list of clinical laboratory tests to be performed and to the SoA (Table 1-1) for the timing and frequency of sampling during the study.

The investigator must review the laboratory report and document this review. The laboratory reports must be filed with the source documents.

Any clinically significant safety findings that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition, are not to be reported as AEs or SAEs.

Venous blood and urine samples are obtained for clinical safety laboratory tests including hematology, clinical chemistry, and urinalysis evaluations. All samples are to be sent to the central laboratory for analysis of the following parameters presented in Appendix 15.4.

In exceptional circumstances, to ensure participant safety and with the sponsor's prior written approval, local laboratory testing may be conducted in lieu of central laboratory testing.

However, central laboratory testing must be retained for PK, biomarkers, and immunogenicity (ADA) samples.

Abnormal laboratory findings discovered during the screening period should be recorded on the medical history page in the eCRF in the form of a diagnosis. Actual laboratory values should not be recorded. All participants with laboratory results with clinically significant abnormal values are followed regularly until the values return to normal ranges or until a valid reason, other than study treatment-related AEs, is identified. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

For laboratory parameters for each panel (hematology, clinical chemistry, urinalysis), please refer to the laboratory manual. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

The local laboratory must be qualified in accordance with local regulations. All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA (Table 1-1).

8.3.3 Physical Examinations

A complete physical examination will be conducted at screening and must include assessment of the cardiovascular, respiratory, gastrointestinal, and neurologic systems, as well as the skin.

Targeted physical examinations may be conducted at study site visits to address intercurrent AEs. Investigators should pay special attention to clinical signs related to previous serious illnesses or concurrent conditions.

8.3.4 Height

Height will be measured at screening and recorded to 1 decimal place without rounding. The instruments used for measuring height should be appropriately and regularly calibrated. Height for adolescents will also be measured whenever vital signs and weight are assessed

according to the SoA (Table 1-1) to evaluate participants' growth over time.

8.3.5 Vital Signs and Weight

Vital signs, including body temperature, respiratory rate (breaths per minute), pulse (beats per minute), and blood pressure (mm Hg), will be obtained with the participant in the seated position, after sitting for at least 5 minutes. Vital sign measurements will be recorded in the eCRF.

Weight will be measured according to the SoA (Table 1-1) and recorded to 1 decimal place without rounding. The instruments used for measuring weight should be appropriately and regularly calibrated. All measurements of weight should be made without shoes and after the removal of any heavy personal items (ie, heavy jewelry, wallets, coats, etc.).

8.3.6 Electrocardiograms

Electrocardiograms will not be performed in this study.

8.3.7 Other Safety Assessments

8.3.7.1 Chest Imaging

Chest x-rays will be conducted as a screening requirement in this study to assess baseline chest health and detect preexisting conditions or abnormalities. A locally performed chest x-ray (posterior–anterior view and, if needed, a lateral view) is required for screening (Visit 1) as specified in the SoA (Table 1-1), unless one has been performed within 12 months of screening (Visit 1) and the report is available for review by the investigator.

For countries that require x-ray for TB assessment, study sites will follow local guidelines. For countries that require an additional TB assessment (ie, QuantiFERON), local guidelines will be followed.

8.3.7.2 Suicidal Ideation and Behavioral Risk Monitoring

Not applicable to this study.

8.3.7.3 Injection Site Reactions

Symptoms of a local ISR may include erythema, induration, pain, pruritus, and edema. If an injection site event is reported, it will be recorded as an AE on the appropriate page in the eCRF.

Additional ISR characterization data will be collected on the ISR-specific page in the eCRF.

8.3.7.4 Systemic Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided in the eCRF on the page specific to systemic hypersensitivity reactions.

Study sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving the study treatment. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples will be collected as described in Appendix 15.5. Laboratory results are provided to the sponsor via the central laboratory.

8.3.7.5 Eosinophil-Related Disorders

A specific eCRF will be used to collect additional data on potential events of eosinophil-related disorders.

The completion of the eCRF page will be conducted by the investigator and will be triggered by:

- Any TEAE of eosinophil-related disorder or,
- A laboratory result of severe eosinophilia (eosinophil count >5000 eosinophils/µL)

The objective is to collect sufficient information for an accurate and complete characterization of any eosinophil-related disorders that may be reported during the study.

8.3.7.6 Hepatitis Testing and Monitoring

Hepatitis B Testing

Initial testing for HBV infection includes:

- HBsAg;
- Anti-hepatitis B core; and
- Anti-hepatitis B surface.

As specified in the SoA (Table 1-1), initial testing for HBV infection includes HBsAg and hepatitis B core antibody (HBcAb) for the following reasons:

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and HBcAb is negative, the participant is not excluded.
- If HBsAg is negative and HBcAb is positive, further testing for HBV DNA is required.
    - If the screening HBV DNA is positive, the participant is excluded.
    - If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study as described in the SoA (Table 1-1).

Management of Enrolled Participants with Detectable HBV DNA During the Study

If HBV DNA is detected, IP will be temporarily withheld or study treatment will be permanently discontinued, as described in Section 7.1.2 and Section 7.2.1, respectively, and the participant should be referred for appropriate follow-up medical care.

Hepatitis C Testing

As specified in the SoA (Table 1-1), initial testing for HCV infection includes testing for antibodies to HCV (anti-HCV).

- If anti-HCV is positive, a test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded (Section 5.2).

Participants who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by polymerase chain reaction negative for at least 24 weeks following treatment completion), are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study treatment will be discontinued (Section 7.1), and the participant should receive appropriate follow-up medical care.

8.3.7.7 Hepatic Safety Monitoring, Evaluation, and Criteria for Investigational Product Interruption or Discontinuation

Table 8-1 and Table 8-2 summarize actions to take based on abnormal hepatic laboratory or clinical changes.

Table 8-1 Participants with Normal or Near Normal Baseline (ALT, AST, or ALP <1.5 × ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue IP
ALT or AST ≥3 × ULN	X		
ALP ≥2 × ULN	X		
TBL ≥2 × ULN[b]	X		
ALT or AST ≥5 × ULN	X	X	
ALP ≥2.5 × ULN	X	X	
ALT or AST ≥3 × ULN with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥5 × ULN for more than 2 weeks	X	X	X
ALT or AST ≥8 × ULN	X	X	X
ALT or AST ≥3 × ULN and TBL ≥2 × ULN[b] or INR ≥1.5	X	X	X
ALP ≥3 × ULN	X	X	X
ALP ≥2.5 × ULN and TBL ≥2 × ULN[b]	X	X	X
ALP ≥2.5 × ULN with hepatic signs or symptoms[a]	X	X	X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; IP = investigational product; TBL = total bilirubin; ULN = upper limit of normal.

a. Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, and/or rash.

b. In participants with Gilbert's syndrome the threshold for TBL may be higher.

Table 8-2 Participants with Elevated Baseline (ALT, AST, or ALP ≥1.5 × ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue IP
ALT or AST ≥2 × baseline	X		
ALP ≥2 × baseline	X		
TBL ≥2 × ULN[b]	X		
ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first)	X	X	
ALP ≥2.5 × baseline	X	X	
ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥4 × baseline or ≥400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) and TBL ≥2 × ULN[b] or INR≥1.5	X	X	X
ALP ≥3 × baseline	X	X	X
ALP ≥2.5 × baseline and TBL ≥2 × ULN[b]	X	X	X
ALP ≥2.5 × baseline with hepatic signs or symptoms[a]	X	X	X

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; IP = investigational product; TBL = total bilirubin; ULN = upper limit of normal.

a. Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, and/or rash.

b. In participants with Gilbert's syndrome the threshold for TBL may be higher.

8.3.7.8 Close Hepatic Monitoring

If a participant develops any one of these changes, initiate close hepatic monitoring (Table 8-3).

Table 8-3 Close Hepatic Monitoring

Participants with normal or near normal baseline (ALT, AST, or ALP<1.5 × ULN)	Participants with elevated baseline (ALT, AST, or ALP≥ 1.5 × ULN)
ALT or AST ≥3 × ULN **or**	ALT or AST ≥2 × baseline
ALP ≥2 × ULN **or**	ALP ≥2 × baseline
TBL ≥2 × ULN[a]	TBL ≥2 × ULN[a]

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

a. In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests (Appendix 15.2), including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase, creatine kinase, and complete blood count with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.

- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values.

- In younger adolescents, special care should be taken to minimize the volume of blood taken during hepatic monitoring.

- In addition to the laboratory tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including current symptoms, recent illnesses (eg, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

8.3.7.9 Comprehensive Hepatic Evaluation

If a participant develops any one of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation (Table 8-4).

Table 8-4 Comprehensive Hepatic Evaluation

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5 × ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5 × ULN)
ALT or AST ≥5 × ULN **or**	ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first) **or**
ALP ≥2.5 × ULN **or**	ALP ≥2.5 × baseline **or**
ALT or AST ≥3 × ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥5 × ULN for more than 2 weeks **or**	ALT or AST ≥3 × baseline or ≥250 U/L(whichever occurs first) for more than 2 weeks **or**
ALT or AST ≥8 × ULN **or**	ALT or AST ≥4 × baseline or ≥400 U/L (whichever occurs first) **or**
ALT or AST ≥3 × ULN and TBL ≥2 × ULN[b] or INR≥ 1.5	ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) and TBL ≥2 × ULN[b] or INR≥ 1.5

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

a. Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, and/or rash.

b. In participants with Gilbert's syndrome the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio; tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (eg, ultrasound or CT scan).

- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol.

- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

- Clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until levels normalize or return to approximate baseline values.

- All the medical information and tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded on the hepatic safety page in the eCRF.

8.3.7.10 Investigational Product Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the IP and continue close monitoring and comprehensive hepatic evaluation as described in Table 8-5, Section 8.3.7.7, and Section 8.3.7.8.

Table 8-5 Laboratory or Clinical Changes Resulting in Investigational Product Interruption or Discontinuation

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5 × ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5 × ULN)
ALT or AST ≥3 × ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥5 × ULN for more than 2 weeks **or**	ALT or AST ≥3 × baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks **or**
ALT or AST ≥8 × ULN **or**	ALT or AST ≥4 × baseline or ≥400 U/L (whichever occurs first) **or**
ALT or AST ≥3 × ULN and TBL ≥2 × ULN[b] or INR≥ 1.5 **or**	ALT or AST ≥2 × baseline or ≥250 U/L (whichever occurs first) and TBL ≥2 × ULN[b] **or**
ALP ≥3 × ULN **or**	ALP ≥3 × baseline **or**
ALP ≥2.5 × ULN and TBL ≥2 × ULN[b] **or**	ALP ≥2.5 × baseline and TBL ≥2 × ULN[b] **or**
ALP ≥2.5 × ULN with hepatic signs or symptoms[a]	ALP ≥2.5 × baseline with hepatic signs or symptoms[a]

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

a. Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, and/or rash.

b. In participants with Gilbert's syndrome the threshold for TBL may be higher.

Interruption or discontinuation of IP should include these actions:

- While the participant is not receiving the IP, clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until liver tests normalize or return to approximate baseline values.

- If the hepatic event continues past the anticipated end of the study (ie, data lock) the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study (ie, data lock date).

- All the medical information and test results related to the close hepatic monitoring (Section 8.3.7.8) and comprehensive hepatic evaluation (Section 8.3.7.9) should be collected and recorded on the hepatic safety page in the eCRF.

- Resumption of the IP after interruption for a hepatic reason can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results returned to near baseline and if a self-limited non-IP etiology is identified. Otherwise, the IP should be permanently discontinued.

8.3.7.11 Serious and Opportunistic Infections

Completion of the infection page in the eCRF is required for each infection reported as an AE or SAE (including the common cold). The sponsor will identify infections considered to be opportunistic (Appendix 15.3).

8.4 Pregnancy

Refer to Appendix 15.1 for contraceptive guidance. Pregnancy testing should be performed as described in the SoA (Table 1-1) for pregnancy testing at the study site. WOCPB and all female adolescents will be instructed to take a urine pregnancy test before dosing with IP while away from the study site and to report any positive pregnancy test result while away from their study site to their study site.

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive IP.

- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The

female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

- Any poststudy pregnancy-related SAE considered reasonably related to the IP by the investigator will be reported to the sponsor as described in Section 8.3.1.3. While the investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue the study treatment.

8.5 Pharmacokinetics

Blood samples will be collected for analysis of lebrikizumab PK at time points indicated in the SoA (Table 1-1). Samples will be collected before dosing on a dosing day, and serum concentration of lebrikizumab will be measured.

Procedures for PK sample collection, processing, handling, and shipping will be described in the laboratory manual. Samples will be analyzed at a laboratory approved by the sponsor. Concentrations of lebrikizumab will be assayed using a validated enzyme-linked immunosorbent assay.

Bioanalytical samples collected to measure lebrikizumab concentrations will be retained for a maximum of one year following the last participant visit for the study. During this time, samples remaining after the bioanalysis may be used for exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

Lebrikizumab concentration data that may unblind IP of any participant will not be reported to study sites or to personnel who are blinded to study data unless that participant's treatment arm assignment has been unblinded to facilitate their care. For details of PK sample retention, see Section 12.8.1.

8.6 Pharmacodynamics and Biomarkers

8.6.1 Exploratory Blood and Nasal Biomarkers

Blood and nasal samples will be collected for exploratory biomarker research (eg, CC motif chemokine ligand 17/thymus and activation regulated chemokine, or other cytokines/chemokines).

Biomarker samples will be collected according to the SoA (Table 1-1) and as detailed in laboratory manual provided separately to sites. Samples will be analyzed at a laboratory approved by the sponsor.

These samples may be used for one or more of the following study areas: research on the drug target, variable response to lebrikizumab, mechanisms of action of lebrikizumab, research methods of lebrikizumab or CRSwNP, validating diagnostic tools or assay(s) related to lebrikizumab or CRSwNP, or pathways associated with CRSwNP. For details of sample retention, see Section 12.8.1.

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of lebrikizumab or after lebrikizumab becomes commercially available.

8.6.2 Total Immunoglobulin E

Blood samples will be collected to discern total IgE levels to explore responder variability within the study and to track response variability to lebrikizumab. Samples will be collected according to the SoA (Table 1-1) and as detailed in the laboratory manual provided separately to study sites. For details on sample retention, see Section 12.8.1.

8.7 Immunogenicity Assessments

Blood samples will be collected for analyses of ADA to determine antibody production against lebrikizumab at the time points indicated in the SoA (Table 1-1) and following procedures detailed in the laboratory manual for sample collection, processing, handling, and shipping. For details of immunogenicity sample retention, see Section 12.8.1.

The actual date and time (24-hour clock time) of each sample collection will be recorded. To aid interpretation of results, a blood sample for PK analysis will be collected at the same time points. All samples for immunogenicity should be taken predose when applicable and possible.

Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of lebrikizumab at a laboratory approved by the sponsor. Antibodies may be further characterized by their ability to neutralize the activity of lebrikizumab. Treatment-emergent ADA (TE ADA) are defined in Section 9.5.8.

Immunogenicity data that may unblind any participant to the IP will not be reported to study sites or to personnel who are blinded to study data unless that participant's treatment arm assignment has been unblinded to facilitate their care.

8.8 Medical Resource Utilization and Health Economics

Medical research utilization and health economics parameters are not evaluated in this study.

8.9 Genetics

A whole blood sample will be collected for pharmacogenetic analysis where local regulations allow, according to the SoA (Table 1-1) and following procedures detailed in the laboratory manual for sample collection, processing, handling, and shipping. For details of sample retention, see Section 12.8.1.

Use/Analysis of DNA

- Genetic variation may impact a participant's response to IP, susceptibility to, and severity and progression of disease. Variable response to IP 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 IRB/IEC allow, a sample will be collected to enable potential DNA analysis from consenting participants.

- DNA samples may be used for research related to lebrikizumab or CRSwNP and related diseases. They may also be used to develop tests/assays including diagnostic tests related to lebrikizumab and CRSwNP. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

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

- 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 lebrikizumab continues but no longer than 15 years or other period as per local requirements.

9 Statistical Considerations

This section summarizes the planned statistical analysis strategy and procedures of the CRSwNP study. The details of statistical analysis will be provided in a statistical analysis plan (SAP), which will be finalized prior to unblinding of IP assignments. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the

planned analysis as described in the SAP will be justified and recorded in the clinical study report.

Because all adolescent patients receive lebrikizumab Q2W/Q4W treatment on an open-label basis, no statistical hypothesis will be tested, and no inferential statistical analysis will be performed. Adolescent participants' data will be summarized separately using descriptive statistics and listings based on all observed data. The number and percentage of adolescent participants experiencing ICEs will also be summarized.

All statistical sections below refer to the analysis of adult participants unless otherwise specified.

9.1 Estimands and Intercurrent Events

9.1.1 Intercurrent Events

According to ICH E9(R1) addendum, estimands should be constructed to directly address the ICEs that could affect the interpretation of treatment effect. Therefore, the following ICEs are considered for the primary endpoint analysis of this study (Table 9-1).

Table 9-1 Intercurrent Event Types

Label	ICE Types
ICE1 (Discontinuation of IP)	Discontinuation of IP due to any reasons
ICE2 (Steroid Use – Short-Term)	Short-term use of SCS treatment (1 mg/kg prednisone equivalent per day for ≤7 days of use)
ICE3 (Steroid Use – Long-Term)	Long-term use of SCS treatment (greater use than the definition for short-term use above) or long-term use of nasal saline lavage with corticosteroids (>10 days)
ICE4 (Surgery)	Undergoing nasal polyp surgery
ICE5 (Change to Other Biologics)	Change to another approved biologic therapy for CRSwNP

Abbreviations: CRSwNP = chronic rhinosinusitis with nasal polyps; ICE = intercurrent event; IP = investigational product; SCS = systemic corticosteroids.

Any SCS treatments separated by less than 7 days will be considered continuous treatment. Nasal saline lavage with corticosteroid treatments separated by less than 3 days will be considered continuous treatment.

9.1.2 Estimands

Table 9-2 presents the primary estimand and rationale for strategies to address ICEs.

Table 9-2 Primary Estimand with Rationale for Strategies to Address Intercurrent Events

	Primary Estimand
Estimand Description (summary below)	Differences in means will be compared between participants treated with lebrikizumab and PBO in combination with background INCS, regardless of treatment discontinuation or short-term use of SCS treatment (≤1 mg/kg prednisone equivalent per day for ≤7 days of use). Nasal polyp surgery, change to another approved biologic therapy, or long-term use of SCS or nasal saline lavage with corticosteroids will be considered as treatment failures. In the case of treatment failure, values will be replaced with the worst possible scores.
Endpoint	Primary and key secondary endpoints
Treatment Conditions of Interest	Lebrikizumab versus PBO in addition INCS.
Target Population	Participants with CRS with bilateral NP
Population-Level Summary	Difference in means between lebrikizumab and PBO
ICEs and Strategies to Handle ICEs	
ICE1 (Steroid Use – Discontinuation of IP)	Treatment policy
ICE2 (Steroid Use – Short-Term)	Treatment policy
ICE3 (Steroid Use - Long-Term)	Composite
ICE4 (Surgery)	Composite
ICE5 (Change in Other Biologics)	Composite
Rationale for Strategies	To estimate the treatment effect irrespective of discontinuation of IP and short-term SCS use. The composite strategy is used to set the worst possible score for long-term steroid use, surgery, and change to another approved biologic as this is considered to be treatment failure.

Abbreviations: CRS = chronic rhinosinusitis; ICE = intercurrent event; INCS = intranasal corticosteroid; IP = investigational product; NP = nasal polyp; PBO = placebo; SCS = systemic corticosteroids.

Note: Refer to Table 9-1 for specific numbered ICE definitions.

9.2 Statistical Hypothesis

The following hypotheses will be tested to demonstrate the superiority of lebrikizumab 250 mg Q2W over PBO in reducing study participants' reported nasal congestion along with an objective assessment of NP in participants with CRS with bilateral NP on background therapy with INCS at Week 24.

- Null hypothesis (H10): The mean CFBL in endoscopic NPS at Week 24 for the lebrikizumab 250 mg Q2W group is equal to that for the PBO group.
- Alternative hypothesis (H1a): The mean CFBL in endoscopic NPS at Week 24 for the lebrikizumab 250 mg Q2W group is not equal to that for the PBO group.

and

- Null hypothesis (H20): The mean CFBL in NCS severity at Week 24 for the lebrikizumab 250 mg Q2W group is equal to that for the PBO group.
- Alternative hypothesis (H2a): The mean CFBL in NCS severity at Week 24 for the lebrikizumab 250 mg Q2W group is not equal to that for the PBO group.

9.3 Sample Size Determination

The planned sample size for adults is approximately 510 participants, with 170 participants in the PBO group and 340 participants across the 2 lebrikizumab dose groups. The adult sample size was determined to enable an adequate characterization of the differences in efficacy between lebrikizumab 250 mg Q2W and PBO with regard to mean changes from baseline in NCS severity and endoscopic NPS at Week 24. This planned sample size was calculated based on the treatment effect observed in SINUS-24 and SINUS-52 (Bachert et al 2019) and uses the assumption that the mean difference in CFBL in NCS severity between lebrikizumab and PBO is 0.62 with common standard deviation (SD) 1.0, and the mean difference in CFBL in endoscopic NPS is 1.48 with common SD 2.1. Assuming normal distribution and no negative correlation between the 2 endpoints and 20% dropout rate, a sample size of 170 participants per arm is expected to be sufficient to provide a combined power of 99% using a 2-sided t-test with alpha of 0.01 for changes from baseline in NCS severity and endoscopic NPS at Week 24. In addition to the co-primary endpoints, the sample size also allows sufficient power for the key secondary endpoint of time-to-event for participants

receiving systemic corticosteroids, and/or approved biologics for CRSwNP rescue use, and/or planned surgery. Assuming the probability of having such rescue events during study treatment period is 27% in the placebo group, and is 10% in the lebrikizumab group, with 170 patients per arm, the study will have approximately 90% power to detect a hazard ratio of 0.35 between the treatment groups using a 2-sided log-rank test with alpha of 0.01. The sample size was calculated using nQuery Version 9.1.

Approximately 1020 adult participants will be screened to achieve 510 randomly assigned to IP. The study will use block randomization with fixed block size and be stratified based on 3 factors: asthma and/or AERD versus no asthma/no AERD, prior NP surgery versus no prior NP surgery, geographic region (North America, Europe, rest of the world). Adult participants without asthma and/or AERD history will be limited to approximately 255 participants (out of the total 510 randomized participants). Adult participants without prior surgery will be limited to approximately 255 participants (out of the total 510 randomized participants). Adult participants may fall in more than one category without limitation in numbers.

Adolescents are not included in the above planned sample size and will be enrolled on an open-label basis to the lebrikizumab Q2W/Q4W treatment arm. No specific sample size is targeted for the adolescent population. The study design will allow as many adolescents to be enrolled as possible as long as the adult enrollment period is still open.

9.4 Analysis Sets

The following participant analysis sets will be used in the statistical analyses for adults and adolescents separately. The analysis sets refer to the adult participants only unless otherwise specified. The corresponding adolescent analysis sets follow the same definition of adult analysis sets except for including adolescent participants only, e.g. Adolescent Intent-to-Treat Analysis Set.

All Entered Analysis Set: The All Entered Analysis Set will consist of all participants who sign the ICF as well as all adolescent patients for whom there is informed consent.

Intent-to-Treat (ITT) Analysis Set: The ITT Analysis Set will consist of all participants who are randomized, even if they do not take the assigned treatment, do not receive the correct treatment, or otherwise do not follow the protocol. Participants will be analyzed according to the treatment to which they are assigned. Unless otherwise specified, efficacy and health

outcomes analyses for the induction period will be conducted on this population.

Safety (SAF) Analysis Set: The SAF Analysis Set will consist of participants who are randomized and received at least one dose of either lebrikizumab or PBO. All analyses using the safety set will group participants according to as randomized.

PK Analysis Set: The PK Analysis Set will consist of all participants in the SAF Analysis Set who have at least 1 PK sample analyzed.

PD Analysis Set: The PD Analysis Set will consist of all participants in the SAF Analysis Set who have at least 1 PD sample analyzed.

Immunogenicity Analysis Set: A participant is evaluable for TE ADA if there is at least 1 non-missing test result for ADA for both the baseline and the postbaseline visits.

9.4.1 Description of Subgroups to be Analyzed

The following subgroups will be explored for the primary and key secondary endpoints:

1. Age (<65, ≥65)
2. Sex (male, female)
3. Race (Caucasian, African, Asian, Other)
4. Weight (<80 kg versus. ≥80 kg)
5. Participants with prior surgery
6. Participants with comorbid asthma (including AERD).
7. Region (North America, Europe, rest of world)

Other possible subgroup analyses will be presented in the SAP.

9.5 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarized using the mean, SD, median, minimum value, and maximum

value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings. All confidence intervals (CIs) presented will be 99% (2-sided) CIs for primary and key secondary endpoints.

Full details of the statistical analyses, methods, and data conventions will be described in the SAP.

9.5.1 General Considerations

Data collected in this study will be presented using summary tables, participant data listings and figures. For continuous variables, the number of observations, mean, SD, median, minimum, and maximum will be presented. Categorical variables will be summarized by participant counts and percentages. For ordinal-scaled variables, a combination of presentations may be employed as appropriate: frequency and percentage of observations within a category and means and SDs of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on the N of the analysis set and number of participants with missing data will also be included. For the efficacy and safety analysis during the induction period, the 2 lebrikizumab arms will be pooled and thus there will be 2 treatment groups. Treatment comparisons for the induction period will be made between lebrikizumab Q2W (pooled) versus PBO.

9.5.2 Overview of Statistical Methods: Estimation of Estimands

The primary estimand is a hybrid estimand representing the primary clinical question of interest: what is the difference in means between treatment conditions (lebrikizumab versus PBO), in the target participant population, with NP surgery, change to another approved biologic therapy or long-term use of SCS or nasal saline lavage with corticosteroids considered as treatment failure, regardless of study treatment discontinuation or short-term use of SCS?

Table 9-3 presents a summary of primary statistical methods. Details pertaining to any planned sensitivity and supplementary analyses will be specified in the SAP.

Table 9-3 Summary of Primary Statistical Methods

Estimand Label	Estimand Description	Main Estimation		
		Analysis Set	Censoring Rules	Analysis Model/Method
Primary Estimand	The difference in means in change from baseline compared between participants treated with lebrikizumab and PBO in combination with background INCS, regardless of treatment discontinuation or short-term use of SCS treatment. Short-term use of SCS is defined as ≤1 mg/kg prednisone equivalent per day for less than and equal to 7 days of use. Nasal polyp surgery, change to another approved biologic therapy, or long-term use of SCS or nasal saline lavage with corticosteroids will be considered as treatment failures. In the case of treatment failure, values will be replaced with the worst possible scores.	ITT	Data collected after treatment discontinuation or short-term use of SCS will be included in the analysis. For participants who undergo nasal polyp surgery or change to another biologic therapy or use long-term SCS or nasal saline lavage with corticosteroids, data collected after ICEs will be set to missing and imputed by the worst possible scores. The remaining missing data will be imputed under missing at random assumption (multiple imputation).	ANCOVA with the following covariates in the model: treatment group, baseline value, and stratification factors. Type III tests for LS means will be used for statistical comparison between treatment groups.

Abbreviations: ANCOVA = analysis of covariance; INCS = intranasal corticosteroid; ICE = intercurrent event; ITT = intent-to-treat; LS = least squares; PBO = placebo; SCS = systemic corticosteroids.

9.5.3 Analysis of Co-Primary Efficacy Endpoints

9.5.3.1 Main Estimation of Co-Primary Endpoints

Refer to Table 9-3 for main estimation of the primary estimands for endoscopic NPS and NCS severity.

9.5.3.2 Sensitivity and Supplementary Analysis for Co-Primary Endpoints

Details pertaining to any planned sensitivity and supplementary analysis will be specified in the SAP.

9.5.3.3 Analysis for Supportive Estimands

Details pertaining to any planned supportive estimand will be specified in the SAP.

9.5.4 Analysis of Key Secondary Efficacy Endpoints

For assessments of key secondary efficacy endpoints, treatment comparisons will be made using analysis of covariance with the following in the model: treatment group, baseline value, and stratification factors. Type III tests for least squares (LS) means will be used for statistical comparison between treatment groups. The LS mean difference, standard error, *P* value, and 99% CI, unless otherwise specified, will also be reported.

Proportion of and time-to-event for participants receiving SCS, approved biologics for CRSwNP rescue use, or planned surgery of NP during study treatment period will be derived and analyzed using the Cox proportional hazards model and log-rank test stratified by stratification factors, by considering the first rescue event (defined as any SCS use, approved biologics for CRSwNP, or surgery [actual or planned] for NP) as the event of interest. The estimates of the hazard ratio and corresponding 99% CI will be provided for lebrikizumab Q2W/Q4W Arm versus PBO and lebrikizumab Q2W/Q8W Arm versus PBO.

9.5.5 Analysis of Other Secondary Efficacy Endpoints

The primary efficacy endpoint will be complemented by a wide range of descriptive efficacy analyses. For the other secondary endpoints, all results will be interpreted descriptively for the treatment groups and for each study visit time point (if applicable). Results from the comparative analysis along with CI will be reported. Details of the analysis of other secondary efficacy endpoints will be described in the SAP.

9.5.6 Analyses of Exploratory Efficacy Endpoints

Analyses of exploratory efficacy endpoints will be specified in the SAP.

9.5.7 Pharmacokinetic Analyses

Lebrikizumab PK data will be summarized using descriptive statistics.

Data from this study may be combined with data from other studies to better characterize the PK of lebrikizumab, as well as to explore the relationship between exposure and efficacy and/or safety outcomes. In this case, a separate PK analysis plan will be developed, and the results of these analyses will be described in a separate PK report.

9.5.8 Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with TE ADA against lebrikizumab may be reported.

TE ADA are defined as:

- Treatment-induced ADA: those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADA were detected at baseline, or
- Treatment-boosted ADA: those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADA were detected at baseline.

For the TE ADA+ participants, the distribution of maximum titers may be reported.

The frequency of neutralizing antibodies against lebrikizumab, if performed, may be reported in TE ADA+ participants.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to lebrikizumab may be assessed.

Additional details may be provided in the SAP.

9.5.9 Safety Analyses

All the safety analysis will be based on the SAF Analysis Set.

AEs will be coded using MedDRA. The number and percentage of participants reporting TEAEs, treatment-emergent SAEs including deaths, TEAEs considered related to study treatment, and TEAEs leading to discontinuation from IP will be tabulated by treatment group, system organ class (SOC) and preferred term. The TEAEs by maximum severity and relationship will also be tabulated by treatment group, SOC, and preferred term. AEs, SAEs, deaths, and AEs leading to discontinuation will be listed by participant.

Descriptive statistics for laboratory test results (hematology, clinical chemistry, and urinalysis) will be provided for the observed values and changes from baseline at each scheduled visit. A shift table (abnormal low/normal/abnormal high) will be provided for select laboratory tests.

Descriptive statistics by treatment group will be provided for the observed values and CFBL at each scheduled visit with vital signs assessment.

Results of the physical examinations will be summarized by visit using appropriate descriptive statistics.

9.5.10 Exposure and Compliance

9.5.10.1 Investigational Product Exposure and Compliance

The extent of exposure to the IP in each treatment group will be summarized by total number of days of exposure and total number of injections. Percentage of compliance for a participant will be defined as the number of injections administered divided by the total number of injections the participant was expected to take during the treatment period. A participant will be considered compliant with the dosing regimen if the participant received **≥75%** of the expected number of injections while enrolled in the study.

9.5.10.2 Background Medication Compliance

Compliance for protocol-specified background medication will be calculated for each participant. Percentage of compliance is defined as the number of days when the participant is compliant to the prescribed background medication regimen divided by the number of days the participant stays in the treatment period.

9.5.11 Other Analyses

Summary statistical analyses will be provided for demographics, baseline disease characteristics, medical history, and other characteristics.

Participant disposition will be summarized by treatment or by treatment sequence for each period and include the number of participants in the ITT Analysis Set who completed or withdrew from treatment for each period, as well as the number of participants in each analysis set.

The number of participants who withdrew from IP and withdrew from study will be summarized by treatment or by treatment regimen for each period and the reason for withdrawal.

Medical history will be coded according to the latest version of MedDRA and will be summarized by SOC and preferred term.

The number and percentage of participants with prior and concomitant medications will be tabulated by Anatomical Therapeutic Chemical Classification System of WHO Drug Global dictionary, preferred term, and actual treatment received (or treatment sequence). A medication's usage will be considered concomitant if it was started or continued after the first administration of the IP. If the start date is missing, it will be assumed that the medication was used concomitantly. Details on handling partial dates (ie, year or only year and month) will be described in the SAP.

9.6 Handling of Missing Data

The primary method of handling ICEs and missing data for primary and key secondary endpoints will be aligned with the primary estimand.

- Data collected after treatment discontinuation or short-term use of SCS will be included in the analysis.

- For participants who undergo NP surgery, change to another biologic therapy or use long-term SCS or nasal saline lavage with corticosteroids, data collected after the ICEs will be set to missing and imputed by the worst possible score.

Multiple imputation will be used to handle the remaining missing data. The SAS PROC MI will be used to conduct the multiple imputation. Each complete dataset will be analyzed with the specified analysis. The results from these analyses will be combined into a single inference.

9.7 Interim Analyses

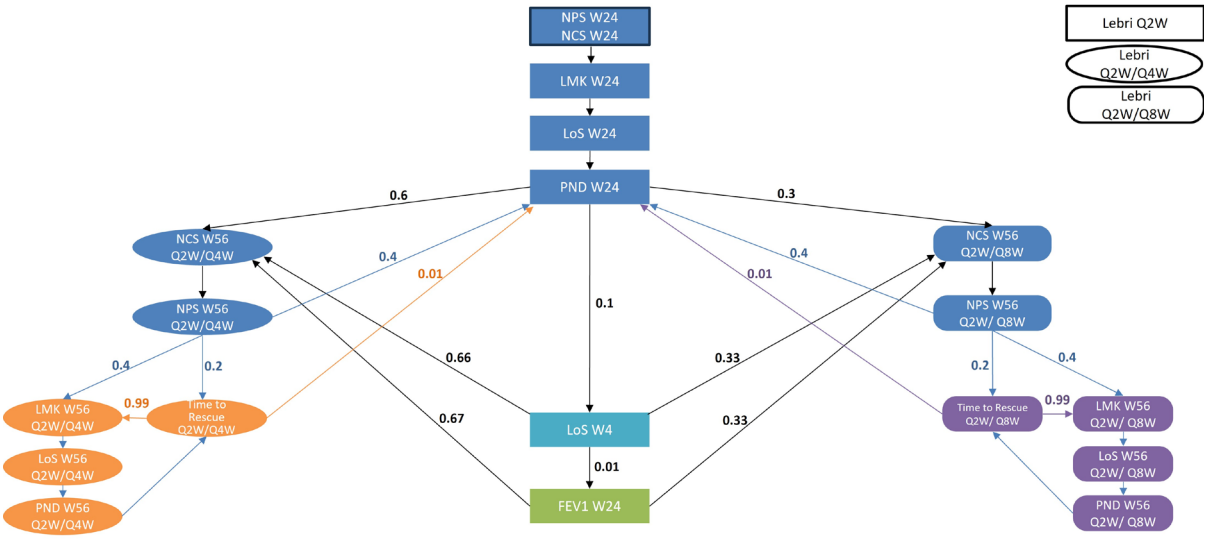
No interim analysis will be performed.

9.8 Multiple Comparisons and Multiplicity

Multiplicity adjusted analyses will be performed on the co-primary and key secondary objectives for the adult participants to control the overall family-wise Type I error rate at a 2-sided alpha level of 0.01. The graphical multiple testing procedure described in Bretz et al. (2009, 2011) will be used. This approach is a closed testing procedure; hence, it strongly

controls the family-wise error rate across all hypotheses (Alosh et al 2014). Figure 9-1 illustrates the current graphical testing procedure. Details of the final graphical testing scheme (including testing order, interrelationships, Type I error allocation for the co-primary and key secondary objectives, and the associated propagation) will be prespecified in the SAP prior to database lock. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside the co-primary and key secondary objectives.

Figure 9-1 Graphical Approach to Control Type I Error Rate for the Adult Participants



9.9 External Data Monitoring Committee

Not applicable to this study.

10 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk (ICH Q9[R1]). The sponsor assumes accountability for actions delegated to other individuals, eg, contract research organizations (CROs).

Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be

monitored during the study and important excursions from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.

10.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports.

Data will be collected via eCRFs, and data must be entered into eCRFs in English. Designated study site staff must complete eCRFs as soon as possible after a participant visit, and the forms should be available for review at the next scheduled monitoring visit. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized site staff. Discrepancies in the data will be brought to the attention of the clinical team and study site staff, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

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

Monitoring details describing strategy (eg, 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 noncompliance issues and monitoring techniques are provided in the monitoring plan.

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

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. AE terms will be coded using MedDRA and concomitant medications will be coded using the WHO Drug Global dictionary.

10.1.1 Electronic Data Capture of Clinical Outcome Assessment

All PROs conducted at the study site will be captured on an electronic tablet during study site visits. All PRO assessments captured away from the study site will be captured in the participants' eDiaries.

The tablets at the study site will be programmed to capture the following PROs, which will be completed by participants during study site visits according to the SoA (Table 1-1):

- VAS of CRS severity (Section 8.2.9)
- PGI-S scales (Section 8.2.17)
- PGI-C scales (Section 8.2.17)
- SNOT-22 (Section 8.2.10)
- ACQ-6 (Section 8.2.12, in asthma participants only)
- PROMIS Short Form v1.0 – Anxiety 8a (Section 8.2.16.1)
- PROMIS Short Form v1.0– Depression 8a (Section 8.2.16.2)
- WPAI+CIQ:CRSwNP (Section 8.2.15)
- EQ-5D-5L (Section 8.2.14)

The PROs will be completed by participants using an on-site tablet in the following order: VAS of CRS severity, PGI-S: nasal congestion, PGI-S: loss of smell, PGI-S: postnasal drip, PGI-C: nasal congestion, PGI-C: loss of smell, PGI-C: postnasal drip, SNOT-22, ACQ-6, PROMIS Anxiety, PROMIS Depression, WPAI+CIQ:CRSwNP, and EQ-5D-5L.

The eDiaries will be programmed to capture the following PROs and other study data:

- NCS (Section 8.2.1)
- Loss of smell (Section 8.2.5)
- Postnasal drip (Section 8.2.6)

- Loss of taste (Section 8.2.8)
- Facial pain/pressure (Section 8.2.8)
- Rhinorrhea (Section 8.2.8)
- IP dosing diary (Section 6.1.2)
- Background medication dosing diary (Section 6.10.2.2)

The PROs should be completed by the participant in their eDiary in the following order: NCS, loss of smell, postnasal drip, loss of taste, facial pain/pressure, and rhinorrhea.

11 Ethics

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice (GCP), and all applicable regulations. The study will be conducted in the EU under Regulation (EU) No. 536/2014.

11.1 Institutional Review Board or Independent Ethics Committee

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before human participants participate in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of participants, and any other written information regarding this study to be provided to the participant must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the study site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date of approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

11.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

11.3 Participant Information and Consent

A written informed consent in compliance with all countries participating in the study shall be obtained from each participant before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant. A study-specific master ICF will be provided by the sponsor to study sites. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the ICF will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participants must be reconsented by signing the revised ICF.

Before recruitment and enrollment, each prospective adult participant or parental/legal guardian of an adolescent participant will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the investigator is assured that the adult participant or parental/legal guardian of an adolescent participant understands the implications of participating in the study, the adult participant or parental/legal guardian of an adolescent participant will be asked to give consent to participate in the study by signing the ICF. The authorized person obtaining the informed consent also signs the ICF.

Adolescent participants must also understand the nature of the study and sign an informed assent document prior to receiving any study-related procedures as required by local regulations.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research (if applicable) and explain/address the exploratory research portion of the study. Participant medical records need to state that written informed consent was obtained.

The investigator shall retain the signed original ICFs and give a copy of the signed original form to the participant.

11.3.1 Withdrawal of Consent for the Use of Research Samples

Participants may withdraw their consent for their samples to be stored for research (Section 12.8.1). Details of the sample retention for research will be presented in the ICF.

12 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

12.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, regulatory authorities, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor, or its designee, must be obtained for the disclosure of any said confidential information to other parties.

12.2 Data Protection

The key to protecting the privacy of participants is the principle of data minimization, as represented by the pseudonymization or "key coding" of clinical data related to participants. Wherever a stakeholder in a study can perform their function with access only to key-coded data, then this control is implemented. Only the principal investigator, or designee, has access to fully identified participants' clinical data held in source documents, and they maintain the table that links participant identity to the allocated participant number (ie, key code).

Other stakeholders, including monitors and contracted clinical and technology vendor personnel, may need access to participant identity to perform their specific function, including stakeholders supportive of televisits, home health, direct-to-from-participant

clinical supplies, remote source data verification, electronic consent, and eCOAs. Further to the principle of data minimization in which a stakeholder needs access to participant identity, but not information directly or indirectly indicative of a medical condition, this information is restricted. Study site, sponsor, and vendor processes and controls will regulate the unauthorized disclosure of prohibited participant identifier, including appropriate remedial actions to delete prohibited participant identifier on receipt and in downstream systems, supported by reminders to stakeholders and staff training.

Systems, applications, and technologies will be 21 Code of Federal Regulations (CFR) Part 11 compliant as necessary. Data protection and privacy laws, including the European Union General Data Protection Regulation (GDPR) and the Security Rule of US Health Insurance Portability and Accountability Act, mandate stakeholders to adopt measures designed to protect the confidentiality of regulated personal information. Such measures will include contractual obligations placed among and between stakeholders (eg, study sites, sponsors) and upon any clinical vendors. These are supported by information security assessments of systems, and quality and security audits where required. Expected measures will include technical and organizational controls to prevent unauthorized access, disclosure, dissemination, and alteration or loss of personal information.

Data protection and privacy laws describe and regulate security breaches involving the compromise of regulated personal information. Stakeholders in clinical studies, including study sites, sponsors, CROs, and vendors, will have policies and procedures in place to respond to breaches, including the education of staff on necessary surveillance measures, immediate steps to take to control and investigate breaches, and the arrangement for any legally mandated notification to participants or regulatory authorities, particularly in circumstances where there is potential harm to data participants. In all cases, appropriate privacy and security personnel, including the GDPR Data Protection Officer, are to be involved.

12.3 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR Part 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the participant's disease.

12.4 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and Title 21 of the CFR by providing all essential documents, as follows:

- Protocol and amendments;
- Development safety update report and updates;
- IB and amendments;
- New or revised recruiting materials; and
- Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical study.

An investigator who is participating in an US Investigational New Drug study outside the US needs to sign a Form FDA 1572 waiver prior to enrolling participants at the study site.

12.5 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of participants begins.

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

12.6 Adverse Events and Study Report Requirements

The investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol Section 8.3.1.3.1 and Section 8.3.1.3.2. In

addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

12.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory agencies with any reports required.

12.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of lebrikizumab. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the sponsor.

12.8.1 Long-Term Retention of Samples for Additional Future Research

Sample retention enables the use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of lebrikizumab or after lebrikizumab becomes commercially available. Use of samples for these purposes may begin at any time during the study or the poststudy retention period (Table 12-1).

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research.

Table 12-1 Retention Periods for Different Sample Types

Sample Type	Custodian	Retention Period After Last Participant Visit[a]
Biomarkers	Sponsor or Designee	15 years
Pharmacokinetic	Sponsor or Designee	1 year
Genetics	Sponsor or Designee	15 years
Immunogenicity	Sponsor or Designee	15 years

[a] Retention periods may differ locally.

12.9 Publications and Results Disclosures

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

13 Study Management

The study administrative structure will include PPD (a Thermo Fisher Scientific company) as the CRO, and third party vendors and laboratories.

13.1 Monitoring

13.1.1 Monitoring of the Study

This study will be monitored according to an approved monitoring plan based on the objectives, purpose, design, and complexity of the study. The investigator will allocate adequate time for all monitoring visits and between visits to facilitate the requirements of the study and study timelines. The investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory), phone, fax, and internet and has adequate space to conduct the monitoring visit. Site monitoring is conducted to ensure that the rights of human participants are protected, that the study is implemented in

accordance with the protocol and/or other operating procedures, and that the study uses high-quality data collection processes. The medical monitor will evaluate study processes based on Lilly or designee standards, ICH E6, and all applicable, regulatory guidelines.

13.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory agencies and promptly forward copies of any audit reports received to the sponsor.

13.2 Management of Protocol Amendments and Deviations

13.2.1 Modification of the Protocol

Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the sponsor or designee. Amendments to the protocol (including emergency changes) must be submitted in writing to the investigator's IRB/IEC, along with any applicable changes to the ICF, for approval before participants can be enrolled into an amended protocol.

13.2.2 Protocol Deviations

Protocol deviations are defined as any unplanned differences from the approved protocol. Minor protocol deviations are defined as any unplanned differences from the approved protocol that do not result in harm to the participants, do not significantly affect the scientific value of study data, and do not compromise the integrity or quality of study data. A major protocol deviation is defined as any departure from the approved protocol that impacts the safety, rights, and/or welfare of the participant; negatively impacts the quality or completeness of the data; or makes the informed consent document/form inaccurate.

Deviations, protocol waivers, or exemptions from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study,

regulatory acceptability, or participant safety. Therefore, adherence to the eligibility criteria as specified in the protocol is essential.

The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard/safety risk to participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory agencies, where required.

In order to keep deviations from the protocol to a minimum, the investigator and relevant site staff will be trained in all aspects of study conduct by the sponsor/sponsor representative. This training will occur either as part of the investigator meeting or study site initiation. Ongoing training may also be performed throughout the study during routine study site monitoring activities.

13.2.3 Study-Level Safety Review

Blinded study-level safety reviews will be conducted at periodic intervals throughout the study. These monitoring and risk-mitigation actions, along with regular review of AEs and laboratory data, will assist in the evaluation and management of potential risks associated with lebrikizumab administration.

13.3 Study Termination

Although the sponsor has every intention of completing the study, the sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last visit (includes the SFU visit).

The investigator may initiate study 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:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study drug development.

If the study is prematurely terminated or suspended, the sponsor or designee shall promptly inform the investigators, the IECs/IRBs, the regulatory agencies, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

The decision and reason for study termination will be communicated in writing by the Sponsor to the Investigators and request that all patients will be discontinued. Patients should be scheduled for an Early Termination visit. The entire study will be stopped if:

- Evidence has emerged that, in the collective opinion of the Investigators at each site with the concurrence of the Sponsor, or the sole opinion of the Sponsor, continuation of the study is unnecessary or unethical
- The stated objectives of the study are achieved
- The Sponsor discontinues the development of the study drug

All data available for the patient at the time of study discontinuation must be recorded in the patient's records and the eCRF.

13.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the final data are summarized and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications (as applicable) meet the standards of the ICH harmonised tripartite guideline E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided

reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the final report, the sponsor will provide the investigator with the summary of the study results. The investigator is encouraged to share a summary of the results with the participants, as appropriate. The study results will be posted on publicly available clinical study registers.

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15 Appendices

15.1 Contraceptive Guidance

Adult and adolescent females are considered WOCBP unless they are WNOCBP.

Females are considered WNOCBP if they:

- Have a congenital anomaly such as müllerian agenesis resulting in confirmed infertility;
- Are infertile due to surgical sterilization; or
- Are postmenopausal.

Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.

The postmenopausal state is defined as a woman:

- At any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or
- Aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone level ≥40 mIU/mL; or
- 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
- Aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

[a] Women **should not** be taking medications during amenorrhea such as oral contraceptives, hormonal replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Females on HRT and those whose menopausal status cannot be confirmed will be required to comply with protocol contraception requirements if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraceptive Guidance:

No male contraception is required except in compliance with specific local government study requirements.

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

Agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males, and not plan a pregnancy during the study	• Use periodic abstinence methods
	  ○ Calendar
	  ○ Ovulation
	  ○ Symptothermal, or
	  ○ Postovulation
	• Declare abstinence just for the duration of a study, or
	• Use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Contraception	Agree to use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception. These methods of contraception must be used for the duration of the study.

Examples of different methods of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• Fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization) Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the definition above. • Combination oral contraceptive pill • Progestin-only contraceptive pill (mini-pill) • Implanted contraceptives • Injectable contraceptives • Contraceptive patch (only women <198 pounds or 90 kg) • Total abstinence • Vasectomy (for men in clinical studies and for female partner if only sexual partner) • Fallopian tube implants (if confirmed by hysterosalpingogram)

Methods	Examples
	• Combined contraceptive vaginal ring, or • Intrauterine devices
Effective contraception	• Male or female condoms with spermicide • Diaphragms with spermicide or cervical sponges • Barrier method with use of a spermicide o Condom with spermicide o Diaphragm with spermicide, or o Female condom with spermicide Note: Male and female condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• Spermicide alone • Periodic abstinence • Fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • Withdrawal • Postcoital douche, or • Lactational amenorrhea

15.2 Liver Safety: Suggested Actions and Follow-Up Assessments

Refer to Section 8.3.7.7 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs)	Alkaline phosphatase
Leukocytes (WBCs)	Alanine aminotransferase
Differential:	Aspartate aminotransferase
Neutrophils, segmented	Gamma-glutamyl transferase
Lymphocytes	Creatine kinase
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
International normalized ratio	Ethanol
Prothrombin time	Haptoglobin
Serology	Immunoglobulin A; quantitative
HAV testing:	Immunoglobulin G; quantitative
HAV total antibody	Immunoglobulin M; quantitative
HAV IgM antibody	Phosphatidylethanol
HBV testing:	**Urine Chemistry**
Hepatitis B surface antigen	Drug screen
anti-HBs	Ethylglucuronide
anti-HBc	**Other Serology**
Hepatitis B core IgM antibody	Antinuclear antibody
Hepatitis B core IgG antibody	ASMA[a]
HBV DNA[d]	Anti-actin antibody[b]
HCV testing:	EBV testing:
HCV antibody	EBV antibody
HCV RNA[d]	EBV DNA[d]
HDV testing:	CMV testing:
HDV antibody	CMV antibody
HEV testing:	CMV DNA[d]

Hematology	**Clinical Chemistry**
HEV IgG antibody	HSV testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[d]	HSV (Type 1 and 2) DNA[d]
Microbiology[c]	Liver kidney microsomal-1 antibody
Culture:	
Blood	
Urine	

Abbreviations: ASMA = anti-smooth muscle antibody; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; RBC = red blood cell; WBC = white blood cell.

a. Not required if anti-actin antibody is tested.

b. Not required if ASMA is tested.

c. Assayed ONLY by investigator-designated local laboratory; no central testing available.

d. Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

15.3 Examples of Infections That May Be Considered Opportunistic

The following are examples of infections that may be considered opportunistic in the setting of biologic therapy (adapted from Winthrop et al 2015). This table is provided to aid the investigator in recognizing infections that may be considered opportunistic in the context of biologic therapy. This list is not exhaustive. Infections will be categorized by Lilly as opportunistic according to *Opportunistic Infections and Biologic Therapies in Immune-Mediated Inflammatory Diseases: Consensus Recommendations for Infection Reporting during Clinical Trials and Postmarketing Surveillance* by Winthrop et al 2015.

Bacterial	
	Bartonellosis (disseminated disease only)
	Campylobacteriosis (invasive disease only)
	Legionellosis
	Listeriosis (invasive disease only)
	Nocardiosis
	Tuberculosis
	Non-tuberculous mycobacterial disease
	Salmonellosis (invasive disease only)
	Shigellosis (invasive disease only)
	Vibriosis (invasive disease due to *Vibrio vulnificus*)
Viral	
	BK virus disease including polyomavirus-associated nephropathy
	Cytomegalovirus disease
	Hepatitis B virus reactivation
	Hepatitis C virus progression
	Herpes simplex (invasive disease only)
	Herpes zoster (any form)
	Post-transplant lymphoproliferative disorder (Epstein-Barr virus)
	Progressive multifocal leukoencephalopathy, John Cunningham (JC) virus
Fungal	
	Aspergillosis (invasive disease only)
	Blastomycosis
	Candidiasis (invasive disease or oropharyngeal, esophageal. Not isolated lingual)
	Coccidioidomycosis
	Cryptococcosis
	Histoplasmosis
	Paracoccidioides infections
	Penicilliosis
	Pneumocystosis
	Sporotrichosis

	Other invasive molds: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor,* and *Lichtheimia*), *Scedosporium*/*Pseudallescheria boydii*, *Fusarium*
Parasitic	
	Leishmaniasis (visceral only)
	Strongyloidiasis (hyperinfection syndrome or disseminated disease)
	Microsporidiosis
	Toxoplasmosis
	Trypanosoma cruzi infection (Chagas disease progression) (disseminated disease only)
	Cryptosporidiosis (chronic disease only)

Source: Adapted from Winthrop et al 2015.

15.4 Clinical Laboratory Tests

General guidance for clinical laboratory testing (Table 15-1) includes the following:

- The tests detailed in the table below will be performed by the central laboratory.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Provision of Laboratory Test Results

Laboratory results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

Laboratory Test Prioritization to Minimize Blood Sampling

Care should be taken to safeguard study participants with regard to the frequency and blood volume amount collected for study procedures. Efforts have been made to minimize the blood sampling required by this protocol. However, the following guidance is provided to assist sites in further minimizing when deemed necessary by investigator discretion or according to local requirements. Sites should follow local IRB guidelines, where applicable.

If there is a concern with participant(s) weight, please contact the medical monitor for further guidance.

In the situation where blood volume is limited and/or safety is of concern, and all tubes cannot be collected, please prioritize sample collections as follows:

1. Clinical chemistry;

2. Hematology;
3. Serum pregnancy;
4. Hepatitis screening (HCV antibody, HBcAb, HBsAg, and hepatitis B surface antibody);
5. HIV;
6. HBV DNA;
7. HCV RNA;
8. PK;
9. Immunogenicity (ADA);
10. Exploratory biomarkers (includes IgE);
11. Genetics; and
12. Hypersensitivity.

Please refer to the laboratory manual for collection tube volumes for each of the above mentioned tests.

Special care should be taken to minimize the volume of blood taken during hepatic monitoring and/or a systemic hypersensitivity event. The medical monitor should be contacted for guidance.

Table 15-1 Clinical Laboratory Tests

Clinical Laboratory Tests	Comments
Hematology	Assayed by the central laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs)	
Mean cell volume	
Mean cell hemoglobin	

Clinical Laboratory Tests	Comments
Mean cell hemoglobin concentration	
Leukocytes (WBCs)	
Differential	
Percent and absolutes count of:	
Neutrophils, segmented	
Neutrophils, bands	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	
Absolute neutrophil count (Calculation) (Definition - include segs and bands or segs, bands, and other immature cells)	
Clinical Chemistry	Assayed by the central laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase	
Alanine aminotransferase	
Aspartate aminotransferase	
Gamma-glutamyl transferase	
Blood urea nitrogen	
Creatinine	
Creatine kinase	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose (nonfasting)	

Clinical Laboratory Tests	Comments
Hormones (female)	
Serum pregnancy	Assayed by the central laboratory.
Urine pregnancy	Evaluated locally.
HIV and Hepatitis Serology	Assayed by the central laboratory.
HIV testing	
HCV testing:	
HCV antibody	
HCV RNA	Performed only for participants who test positive for HCV antibody.
HBV testing:	
HBV DNA	Performed only for participants who test positive for HBcAb.
HBcAb	
HBsAg	
HBsAb	
Pharmacokinetic Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the study sites.
LY3650150 concentration	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the study sites.
Anti-LY3650150 antibodies	
Anti-LY3650150 antibodies neutralization	
Genetics Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the study sites.
Exploratory Biomarker Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the study sites.
Whole blood	
Plasma	
Serum	
Nasal brushing	
Hypersensitivity Tests and/or Infusion-Related Reaction (as appropriate)	Assayed by the central laboratory. Results will not be provided to the study sites.
Hepatic Monitoring	Assayed by the central laboratory. Results will not be provided to the study sites.
Hepatic Monitoring	Assayed by central laboratory. Results will not be provided to the study sites.
Urinalysis	Assayed by central laboratory.
Bilirubin	

Clinical Laboratory Tests	Comments
Glucose	
Ketones	
Leukocytes esterase	
Nitrites	
Occult blood	
pH	
Protein	
Specific gravity	
Urobilinogen	

Abbreviations: HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; RBC = red blood cell; WBC = white blood cell.

15.5 Recommended Laboratory Testing for Systemic Hypersensitivity Events

Purpose of Collecting Samples After a Systemic Hypersensitivity Event

The samples listed in this attachment are not collected for acute study participant management. The sponsor will use the laboratory test results from these samples to characterize hypersensitivity events across the clinical development program.

When to Collect Samples After a Systemic Hypersensitivity Event Occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized. Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess postevent return-to-baseline values.

Timing	Laboratory[a] Test
Collect from 30 minutes to 4 hours after the start of the event. • Note: The optimal collect time is from 1 to 2 hours after the start of the event.	Total tryptase
Collect only if not already collected on the same day as the event. • Note: If collecting, collect up to 12 hours after the start of the event.	Ly3650150 antidrug antibodies LY3650150 concentration

[a.] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What Information to Record

Record the date and time when the samples are collected.

Allowed Additional Testing for Participant Management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

15.6 Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this Appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional Circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing Changes Under Exceptional Circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local IRB/IEC, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (eg, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for Making a Change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed Consent

Additional consent from the adult participant and parent/legal guardian of adolescent participants (and adolescent participant assent) will be obtained, if required, for:

- Participation in remote visits;
- A change in the method of study treatment administration;
- Dispensation of additional study treatment during an extended treatment period;
- Alternate delivery of study treatment and ancillary supplies; and
- Provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional Circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

- **Remote visits:** In source documents and the eCRF, the study site should capture the visit location and method, with a specific explanation for any data missing because of missed in-person site visits.
    - Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, check of concomitant medications and AEs.
    - Mobile healthcare: If written approval is provided by the sponsor, healthcare visits may be performed by a mobile healthcare provider at locations other than the study site (eg, satellite sites affiliated to the hospital) when participants cannot travel to the site due to an exceptional circumstance.
        - Procedures performed at such visits include, but are not limited to, collection of blood and urine samples, physical assessments, AEs, and concomitant medications.

- Measurement of vital signs and body temperature may be possible if the equipment used at the site is mobile or similar validated equipment is available at alternative locations.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

- **Local laboratory testing option:** Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for:
  - LKM-1 antibodies;
  - LY3650150 concentrations;
  - Anti-LY3650150 antibodies;
  - Anti-LY3650150 antibodies neutralization;
  - Genetic samples;
  - Exploratory biomarker serums; and
  - Long-term storage samples.

The local laboratory must be qualified in accordance with applicable local regulations.

- **Study treatment and ancillary supplies (including participant diaries):** When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:
  - Asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit;
  - Asking the participant's designee to go to the site and receive study supplies on a participant's behalf; and
  - Arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study treatment should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing

protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
    - When delivering supplies to a location other than the study site (eg, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (ie, storage conditions maintained and intact packaging upon receipt).
    - Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

- **Screening period guidance:** To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening are valid for a maximum of 30 days. The following rules will be applied for active, nonrandomly assigned participants whose participation in the study must be paused due to exceptional circumstances.

- If screening is paused for less than 30 days from screening visit to randomization visit, the participant will proceed to the next study visit per the usual SoA (Table 1-1).
    - If the participant's eligibility criteria are confirmed, the site should conduct the next visit and document the reason for delay in the eCRF.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 30 days from screening visit to randomization visit, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the eCRF. This screen failure is allowed in addition to the main protocol screen failure. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA (Table 1-1) should be followed, starting at the screening visit to ensure participant eligibility by randomization visit.

- **Adjustments to visit windows:** Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA (Table 1-1). To maximize the possibility that these visits are conducted on-site, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study. The allowed adjustments to visit windows are described below (Table 15-2).

Table 15-2 Allowed Adjustments to Visit Windows

Visit Number	Tolerance
Visits 3 to 9	Beyond the ±3 days already given in the schedule of activities (Table 1-1), these visits can occur ±7 days from the intended date
Visits 10 to 11	Beyond the ±5 days already given in the schedule of activities (Table 1-1), these visits can occur ±7 days from the intended date
Safety Follow-up	Beyond the ±5 days already given in the schedule of activities (Table 1-1), this visit can occur ±14 days from the intended date

For participants whose visits have extended windows, additional study treatment may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented as follows:

- Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances.
- Dispensing/shipment records of study treatment and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

15.7 Country-specific Requirements – South Korea

This appendix describes changes to be followed in South Korea. The changes were revised in accordance with regulatory requirements and are specific to any investigational site in South Korea.

The revised text in the following sections shows the changes applicable only to participants in South Korea. All deletions have been identified by ~~strikethroughs~~; all additions have been identified by the use of underscore.

15.7.1 Schedule of Activities

Footnote t: For countries that require an additional TB assessment (ie, QuantiFERON)), local guidelines will be followed (see Section 8.3.7.1 for further details).

15.7.2 Exclusion Criteria

Section 5.2.

22. Has had any of the following types of infection within 3 months prior to screening or develops any of these infections during screening or the run-in period:

    a. Serious (requiring hospitalization, and/or intravenous or equivalent oral antibiotic treatment).

    b. Opportunistic (as defined in Winthrop et al 2015, Appendix 15.3).

    Note: Participants with latent TB that are appropriately treated may be considered eligible to participate in the study (South Korea-specific Section 8.3.7.1).

c. Symptomatic herpes zoster infection not resolved at the time of screening. Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over).

d. Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer), other than Chronic Rhinosinusitis.

e. Recurring (including, but not limited to recurring cellulitis, chronic osteomyelitis). Note: Participants with only recurrent, mild, and uncomplicated orolabial and/or genital herpes may be permitted at medical monitor's discretion.

15.7.3 Chest Imaging and Tuberculosis Assessments

Section 8.3.7.1. Chest Imaging and Tuberculosis Assessment

For countries that require x-ray for TB assessment, study sites will follow local guidelines. For countries that require an additional TB assessment (ie, QuantiFERON) local guidelines will be followed.

- TB testing: QuantiFERON, T-SPOT, PPD testing
  Note: For PPD testing, participants should come back to the clinic 48 to 72 hours after test application. Skin induration ≥5 mm in diameter is interpreted as positive for the purpose of this study.
- TB testing is not required at screening for participants with a known diagnosis of latent TB.

  Participants with latent TB should have received at least 4 weeks of prophylaxis treatment prior to screening and must complete the course of treatment during the study (Patients with inadequate treatment such as those with latent TB that were treated for more than 4 weeks but did not complete this course of treatment are not eligible to participate in the study).

Additional requirement for participants that are appropriately treated for latent TB:

- No history of risk of re-exposure since their last treatments were completed
- No evidence of reactivation of latent TB
- Have no evidence of hepatoxicity (ALT and AST levels must remain ≤2 × ULN) upon retesting of serum ALT and AST levels before randomization.

15.7.4 Genetic Sampling and Consent

Section 8.9. Genetics

Genetic sampling will be optional to the participant in South Korea.

Section 11.3. Participant Information and Consent

A separate informed consent (and assent, as applicable) will be signed by participants or their legally authorized representatives for the collection of genetic sampling. Adolescents who reach the age of majority (typically 18 years of age, but legal age may vary depending on regulations of each country) during the study will need to sign a consent in South Korea.

15.8 Country-specific Requirements – Taiwan

This appendix describes changes to be followed in Taiwan. The changes were revised in accordance with regulatory requirements and are specific to any investigational site in Taiwan.

The revised text in the following sections shows the changes applicable only to participants in Taiwan. All deletions have been identified by ~~strikethroughs~~; all additions have been identified by the use of underscore.

15.8.1 Genetics

Section 8.9

Genetic sample collection will not be implemented in Taiwan due to local requirements.

15.9 Protocol Amendment 2 Summary of Changes

Protocol Amendment Summary of Changes

Protocol Version History	
Protocol Version	**Date**
Amendment 2	01 July 2024
Amendment 1	08 December 2023
Original Protocol	17 November 2023

Amendment 2 (01 July 2024**)**

Overall Rationale for the Amendment: The original protocol was updated based on feedback received from the European Medicines Agency (EMA).

Changes from Amendment 1 (08 December 2023) to Amendment 2 (01 July 2024) are summarized in the following table.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 4.1 Overall Design	Clarified that block randomization with fixed block size will be used.	Updated text based on EMA requirements.
Section 8.3.1.1.1 AEs	Added reporting of medication errors and IP use outside what is defined in the protocol (including misuse and abuse) as adverse events per EU regulations.	Updated text based on EMA requirements.
Section 8.3.1.3.2 Reporting Suspected Unexpected Serious Adverse Reactions	Added the procedure for reporting of suspected unexpected serious adverse reactions (SUSAR) in the EU.	Updated text based on EMA requirements.
Section 9.3 Sample Size Determination	Added additional information on the sample size and power calculations and added clarification on block randomization.	Updated text based on EMA requirements.
Section 11 Ethics	Added sponsor statement that the clinical trial will be conducted in compliance with Regulation [EU] No 536/2014.	Updated text based on EMA requirements.
Section 11.1 Institutional Review Board or Independent Ethics Committee, Section 11.3 Participant Information and Consent, Section 12.1 Confidentiality	Removed “or the participant’s legally authorized representative” as no vulnerable populations are included in the trial.	Updated text based on EMA requirements.
Section 13.3 Study Termination	Added clinical trial termination criteria.	Updated text based on EMA requirements.
Section 14 References	Reference added in support of sample size calculation text.	Updated based on EMA requirements.