STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:	A PHASE 3 RANDOMIZED, PLACEBO-CONTROLLED STUDY TO ASSESS SAFETY, TOLERABILITY AND EFFICACY OF GARETOSMAB IN PATIENTS WITH FIBRODYSPLASIA OSSIFICANS PROGRESSIVA
Compound:	REGN2477
Protocol Number:	R2477-FOP-2175 Amendment 5
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Amendment 1 / June 10, 2025

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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAS	ADA analysis set
ACVR1	Type I activin A receptor
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BMI	Body mass index
BMP	Bone morphogenic protein
CAJIS	Cumulative Analog Joint Involvement Scale
CGIC	Clinician's Global Impression of Change
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel (test)
CT	Computed tomography
DBTP	Double-blind treatment period
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ENT	Ear, nose, and throat
EOS	End of study
EQ-5D-3L	EuroQol 5 dimensions questionnaire with a 3-level scale
ET	Early termination
ETP	Extended Treatment Period
ETV	Early termination visit
FBR	Future biomedical research
FCS	Fully conditional specification
FEV1	Forced expiratory volume in 1 second
FOP	Fibrodysplasia ossificans progressiva
FSH	Follicle-stimulating hormone
FDA	US Food and Drug Administration
FVC	Forced vital capacity
GPIIb/IIIa	Glycoprotein IIb/IIIa
HbA1c	Hemoglobin A1c
HGRAC	Human Genetic Resource Administration of China
HO	Heterotrophic ossification
HR	Heart rate
HRQoL	Health-related quality of life
ICF	Informed consent form

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ICH	International Conference of Harmonization
INR	International normalization ratio
IRR	Infusion related reaction
IV	Intravenous
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
LOCF	Last Observation Carried Forward
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenzel
MI	Multiple imputation
PAC-1	Procaspase-activating compound 1
PCSV	Potentially clinically significant value
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PK	Pharmacokinetic
PMM	Predictive mean matching
PT	Preferred term
Q4W	Every 4 weeks
RBC	Red blood Cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RR	Rate ratio
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SF-36	Short-Form 36
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULOQ	Upper limit of quantification
WHODD	WHO Drug Dictionary
WBC	White blood cell
WOCBP	Women of childbearing potential
WOCF	Worst observation carried forward

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1. OVERVIEW

The SAP is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses and analysis presentation to be used for the study specified in protocol R2477-FOP-2175 Amendment 5 dated Sep 24, 2024.

1.1. Study Description and Objectives

R2477-FOP-2175 is a phase 3, randomized, multi-center, multinational, parallel-group, placebo-controlled study to assess the efficacy of garetosmab on the reduction of heterotopic bone formation, and its safety, tolerability, and pharmacokinetics (PK) in fibrodysplasia ossificans progressiva (FOP) patients with active disease caused by any FOP-causing variant of type I activin A receptor (ACVR1).

1.1.1. Primary Objective(s)

The primary efficacy objective of the study is to assess the effect of garetosmab (10 mg/kg, 3 mg/kg) versus placebo on the formation of new HO lesions from baseline to week 56, as determined by low-dose CT.

The primary safety objective of the study is to assess the safety and tolerability of garetosmab (10 mg/kg, 3 mg/kg) versus placebo from baseline to week 56.

1.1.2. Secondary Objective(s)

The key secondary objectives of the study are:

- To assess the effect of garetosmab (10 mg/kg and 3 mg/kg) versus placebo on the number per patient of clinician-assessed flare-up episodes to week 56
- To assess the effect of garetosmab (10 mg/kg and 3 mg/kg) versus placebo on the proportion of patients with new HO lesions as determined by CT at week 56
- To assess the effect of garetosmab (10 mg/kg and 3 mg/kg) versus placebo on volume of new HO lesions as determined by CT at week 56
- To assess the effect of garetosmab (10 mg/kg and 3 mg/kg) versus placebo on the occurrence of patient-reported flare-up episodes through week 56

All other secondary objectives will compare the 10 mg/kg dose group to the placebo group and the 3 mg/kg dose group to the placebo group at week 28 and week 56 unless otherwise specified.

Other secondary objectives of the study are:

- To assess the effect of garetosmab versus placebo on the number of new HO lesions per patient from baseline to week 28 as determined by CT
- To assess the effect of garetosmab versus placebo on the number per patient of clinician assessed flare-up episodes to week 28
- To assess the effect of garetosmab versus placebo on the proportion of patients with new HO lesions as determined by CT at week 28

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- To assess the effect of garetosmab versus placebo on volume of new HO lesions as determined by CT at week 28
- To assess the effect of garetosmab versus placebo on the occurrence of patient-reported flare-up episodes to week 28
- To assess the effect of garetosmab versus placebo on the occurrence of clinician-assessed flare-up episodes
- To assess the effect of garetosmab versus placebo on the number per patient of patient-reported flare-up episodes
- To characterize the concentrations of total activin A
- To evaluate concentrations of garetosmab
- To assess the immunogenicity of garetosmab
- To assess the effect of garetosmab versus placebo in pulmonary function assessed by pulmonary function tests
- To assess clinical outcomes (ie, joint function [Cumulative Analog Joint Involvement Scale (CAJIS)]) at baseline and over time after the first dose of garetosmab versus placebo
- To assess the effect of garetosmab versus placebo on patient's disease severity assessed by the Patient Global Impression of Severity (PGIS)
- To assess the effect of garetosmab versus placebo on patient's change in disease assessed by the Patient's Global Impression of Change (PGIC)
- To assess the effect of garetosmab versus placebo on clinician's change in disease assessed by the Clinician's Global Impression of Change (CGIC)
- To assess the safety and efficacy of garetosmab beyond 12 months

1.1.3. Exploratory Objectives

The exploratory objectives of the study are:

- [redacted]
- [redacted]

1.2. Statistical Hypothesis

Let R_1 be the rate of new HO lesion formation, ie, the mean number of new HO lesions formed per year during the 56 weeks of DBTP for each garetosmab treatment group, and R_2 be the rate of new HO lesion formation for the placebo group. The Rate Ratio (RR) for new HO lesion formation (each dose versus placebo) will be defined as:

$$RR = \frac{R_1}{R_2}$$

The hypothesis that will be tested is: $H_0: RR = 1$ versus $H_1: RR \neq 1$.

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1.3. Interim Analysis/(es)

No interim analyses were planned for this study.

1.4. Modifications from the Statistical Section in the Final Protocol

This section summarizes major changes to the protocol statistical section with emphasis on changes after protocol amendment 5 (dated 24 Sep 2024). These changes are not based on any unblinded study data. The summary of modifications is listed in the following table.

Item	Protocol Section	Description
1	4.2.1. Estimand for Primary Efficacy Objective	SAP Section 7.2.1: Handling of intercurrent event of death for number of new HO lesions at week 56 is changed from [redacted]
2	4.2.2. Estimands for Key Secondary Objectives	SAP Section 7.2.2.1: Handling of intercurrent event of death for total volume of new HO lesions at week 56 is changed from [redacted]

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1.5. Revision History for SAP Amendments

Amendment 1:

SAP Section	Change	Rationale
7.2. Analysis of Efficacy Data	Updated the imputation models for primary and secondary endpoints as applicable to remove age, gender, and the randomization stratification factor of previous participation in LUMINA-1.	[redacted]
7.2.1.1. Sensitivity Analysis	Added the following sensitivity analyses for the primary endpoint: • Multiple Imputation Using Placebo Washout Method • Tipping Point Analysis • Death considered as the worst value among all patients regardless of the treatment group	Per Health Authority request
7.2.2. Analyses of Secondary Endpoints	Binary endpoints will be analyzed using Barnard's exact test rather than Fisher's exact test.	For handling missing data through multiple imputation.
7.2.2.1. Analysis of Key Secondary Endpoints	Added the following sensitivity analyses for the key secondary endpoints, when applicable: • Multiple Imputation Using Placebo Washout Method • Death considered as the worst value among all patients regardless of the treatment group	Per Health Authority request
7.2.2.4. Analysis of Exploratory Endpoints	[redacted]	[redacted]

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	[redacted]	[redacted]
8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL	Added the US-specific testing strategy	Per Health Authority request
Throughout the document	Minor changes made to correct errors or clarify the intended analyses	For clarity

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2. INVESTIGATION PLAN

2.1. Study Design

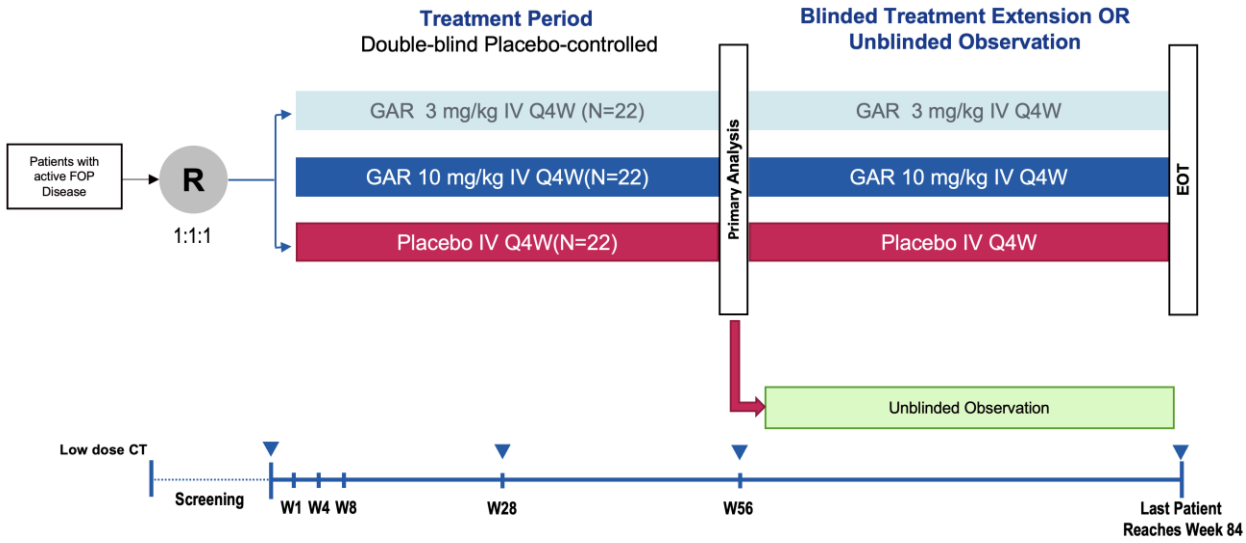
The study consisted of 4 periods and a Follow-up Safety Visit (Figure 1):

- **Screening Period:** 4 weeks in duration (from study day -28 to day -1 [visit 1]). All patients underwent an informed consent process and screening procedures. Screening procedures could be conducted over multiple days.
- **Double-Blind Treatment Period (DBTP):** 56 weeks in duration (from study day 1 [visit 2] to week 56 [visit 17]). All patients were randomized to double-blind treatment with garetosmab 10 mg/kg, garetosmab 3 mg/kg, or placebo.
- **Extended Treatment Period (ETP):** 28+ weeks in duration (study week 56+ [visit 17+]) for those who continued double-blind treatment. Patients who completed the DBTP and elected to extend double-blinded treatment continued until the last global patient reached week 84.
- **Observation Period:** 28+ weeks in duration (study week 56+ [visit 17+]) for those who discontinue from double-blind treatment. Patients who completed the DBTP and elected to become unblinded and stop treatment were followed to assess survival and any pertinent safety events (ie, severe bleeding; Section 3.3.2 in the protocol) since the last contact. The Observation Period continued until the last global patient completed their last study visit. Patients did not receive treatment and could participate in other studies.
- **Follow-Up Safety Visit:** 30 weeks from the last dose administered (study week 84+ [visit 24+]) for all patients who received treatment, except for patients who were unblinded that were treated with placebo (placebo-treated patients unblinded at week 56 [visit 17] did not participate in the Follow-Up Safety Visit). Consisted of a safety follow-up visit 30 weeks after the last study drug administration.

Randomization was stratified by baseline CAJIS score [dichotomized as ≤12; >12] and previous participation in the R2477-FOP-1623 (LUMINA-1) study [yes vs no]. Approximately 66 patients were planned to be randomized 1:1:1 to garetosmab 10 mg/kg, garetosmab 3 mg/kg, or placebo (See Figure 1).

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Figure 1: Study Flow Diagram



2.2. Sample Size and Power Considerations

During the DBTP of 56 weeks as specified for the primary efficacy hypothesis, a sample size of 44 patients (22 patients on garetosmab 10 mg/kg IV Q4W regimen and 22 on placebo) had 90% power to detect a mean rate ratio of 0.13 new HO lesions (garetosmab mean event rate of 0.15 divided by placebo mean event rate of 1.13). This sample size calculation assumed an alpha level of 0.05, 2-tailed hypothesis testing, maximum likelihood method to calculate the variance under the null hypothesis (Zhu et al., 2013), and an overdispersion factor of 1.66 (obtained from a previous garetosmab study). The sample size had been adjusted for a 5% non-evaluable patient rate. With the intent to perform a dose response analysis, 22 additional patients were planned to be randomized into a third treatment group, specifically the garetosmab 3 mg/kg IV Q4W regimen (low dose). Therefore, the total sample size planned for this study was 66 patients.

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3. ANALYSIS SETS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following defines the set(s) of subjects whose data will be used for statistical analysis.

3.1. Full Analysis Set

The primary efficacy analysis set is the full analysis set (FAS) , defined as all randomized patients who have received study drug. Patients in the FAS will be analyzed according to the treatment group allocated by randomization (ie, as-randomized treatment group).

3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who have received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.3. Pharmacokinetic Analysis Sets

The PK analysis set includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug.

3.4. Total Target Analysis Set

The total target analysis set includes all patients who received any study drug (active or placebo) and who had at least 1 non-missing total target concentration following the first dose of study drug.

3.5. Immunogenicity Analysis Sets

The ADA analysis set (AAS) includes all patients who received any amount of study drug (active or placebo) and had at least 1 non-missing ADA result following the first study dose of the respective study drug. The ADA analysis is based on the actual treatment received.

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4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

Unless otherwise stated, the following conventions will be applied when presenting summary level descriptive statistics for data.

Continuous variables will be summarized within each treatment group, presenting the following summary statistics: the number of patients reflected in the calculation (n), mean, standard deviation, 1st quartile (Q1), median, 3rd quartile (Q3), minimum, and maximum.

For categorical data, frequencies and percentages will be displayed for each category.

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5. PATIENT DISPOSITION

5.1. Screening Dispositions

The number of screened patients (i.e. patients who signed the informed consent form (ICF)) , randomized patients (i.e. assigned a randomization number in the IWRS/IVRS system) and patients who discontinue during the screening period as well as the corresponding reason will be presented. The corresponding percentages with respect to the total number of randomized patients will be presented.

5.2. Treatment Period Dispositions

The disposition of all randomized patients during Treatment Period will be displayed by treatment group. The following summaries will be provided for each treatment group and overall (unless otherwise specified):

- The total number of patients randomized, but not receiving study treatment
- The total number of patients who completed the DBTP, defined as week 56 visit performed
- The total number of patients who prematurely discontinued study treatment during the DBTP, and the reasons for discontinuation
- The total number of patients with week 84 visit performed
- The total number of patients who entered ETP, defined as patients who received study treatment at week 56 visit
- The total number of patients who completed the ETP, defined as patients who did not discontinue the study before the last global patient reached week 84
- The total number of patients who prematurely discontinued study treatment during the ETP, and the reasons for discontinuation
- The total number of patients who completed the study
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients in each analysis set

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6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables will be summarized by treatment group and overall based on the FAS:

- Age at screening (year)
- Age categories (<30, ≥30)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Baseline Weight (kg)
- Height (cm)
- Baseline Body mass index (BMI) (kg/m2)
- Baseline BMI categories (<25, ≥25 to <30, and ≥30)

6.2. Baseline Disease Characteristics

The following disease characteristics will be summarized by treatment group and overall based on the FAS:

- FOP Diagnosis findings including age at FOP diagnosed and duration of FOP
- FOP genetic mutation type (classic, other)
- LUMINA-1 patients (yes, no)
- Baseline CAJIS total score
- Baseline CAJIS total score categories (≤12, >12)
- Baseline PGIS
- Number of patient-reported flare-up in last 12 months
- Baseline FEV1
- Baseline FEV1 percentage of predicted
- Baseline FVC
- Baseline FEV1/FVC ratio
- ENT consultation (normal, abnormal)

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6.3. Medical History

Patient medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency and percentage of each medical history will be summarized by SOC and PT for each treatment group, and overall based on the FAS.

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7. EFFICACY DATA

7.1. Description of Efficacy Data

Low-Dose Whole Body CT to Assess New HO Formation

Identification and analysis of new HO lesions is specified in Section 5.4.1 (Quantitative Assessment of New HO Lesions) of the imaging charter: Independent Review Charter – CT Reads. All patients will undergo whole-body low dose CT to assess formation of new heterotopic bone. The CT scans will be performed at screening, week 28, 56, and 84. The week 84 scans are only performed in patients entering the Extended Treatment Period. The details of the imaging analysis procedures are given in the imaging charter. As specified in the imaging charter for the study, the quantitative assessments of the CT are conducted by two blinded independent reviewers. If both reviewers disagree on the number of, presence of, or location of newly identified lesions during the post-baseline period, an adjudicator will select the assessment of either Reviewer 1 or 2. The quantitative assessments done by the reviewer that the adjudicator has selected at week 56 will be used for the statistical analysis for all relevant imaging endpoints. If no adjudication is performed, the assessments by Reviewer 1 will be arbitrarily selected for analysis.

Daily FOP Flare-Up Diary

The FOP Flare-up diary will be used to collect patient-reported flares. It contains 3 sections, a historical flare-up section (baseline assessment), an ongoing flare-up section, and a new flare-up section. Assessment of FOP Flare-up including flare-up location, frequency, and duration, as well as the severity of selected FOP disease signs and symptoms, including pain, swelling, joint stiffness, and decrease in movement which will be rated by patients using a 4-point scale for each (0: no symptoms; 1: mild; 2: moderate; 3: severe). Patients and their caregiver (if applicable) will be trained on its use at the baseline visit and are instructed to record their scores in the e-diary each day throughout the study during the DBTP.

Clinician Flare-Up Assessment (Investigator Assessed)

The Investigator will assess for the occurrence of new flare-ups since the last visit and record the number of new flare-ups at each post-baseline visit in the dedicated clinician flare-up assessment eCRF. When assessing for an FOP Flare-up, major signs and symptoms to be considered by the investigator include but are not limited to swelling, pain, decrease movement, stiffness, and warmth. All FOP Flare-ups will be considered adverse events (AEs). Additional details will be collected via FOP flare-up eCRF for each Flare-up AE, including the associated signs and symptoms, location, any precipitating factors, and treatment.

Cumulative Analog Joint Involvement Scale Score (CAJIS)

The CAJIS is an assessment of 15 major joints; each major joint rated normal unaffected (0), affected (1), or completely functionally ankylosed (2). The total score ranges from 0 to 30. Due to missing joints, the prorated average of the total CAJIS score will be calculated as 15*(total CAJIS score/number of non-missing joints). Also, the prorated average of axial score, upper limb, and lower limb score will be calculated. Physician assessment of joint involvement will be conducted using the CAJIS at screening, week 28, 56, 84, 108, and 112.

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Patient Global Impression of Severity (PGIS)

PGIS is a single item, self-administered questionnaire to assess the patient's global impression of severity. Patients will respond to the questions "In the last 7 days, how would you rate your worst FOP symptoms?" using a 5-level response scale: none (0), mild (1), moderate (2), severe (3), very severe (4). This endpoint will be used to assess disease severity over time and will be used as an anchor to assess meaningful change. At screening, week 28, 56, 84, 108, and 112, patients will rate the severity of their flareup activity during the study.

Patient's Global Impression of Change (PGIC)

PGIC is a single item, self-administered questionnaire to assess the patient's global impression of change. Patients will respond to the questions "Since the start of the study, your FOP symptoms are:" using a 7-level response scale: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7). This endpoint will be used to assess change in disease severity over time and will be used as an anchor to assess meaningful change. At week 28, 56, 84, 108, and 112, patients will rate their impression of change in their flare-up activity during the study.

Clinician's Global Impression of Change (CGIC)

CGIC is a single-item questionnaire to assess the clinician's global impression of change. The investigator/clinician will respond to the questions "Since the start of the study, your patient's FOP symptoms are:" using a 7-level response scale: very much improved (1), much improved (2), minimally improved (3), no change(4), minimally worse (5), much worse (6), very much worse (7). At week 28, 56, 84, 108, and 112, the physician will rate their impression of the change in the patient's flare-up activity during the study.

Pulmonary Function

FVC and FEV1 and the ratio of FEV1/FVC will be determined by spirometry in patients who are able to undergo this procedure at screening, week 28, and 56.

7.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the number of new HO lesions at week 56.

7.1.2. Secondary Endpoints

Key Secondary Endpoints

The key secondary endpoints are:

- Number of clinician-assessed flare-ups through week 56
- Occurrence of new HO lesions at week 56 (Yes/No)
- Total volume of new HO lesions at week 56
- Occurrence of patient-reported flare-ups through week 56 (Yes/No)

Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

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- Number of new HO lesions at week 28
- Number of clinician-assessed flare-ups through week 28
- Occurrence of new HO lesions at week 28 (Yes/No)
- Total volume of new HO lesions at week 28
- Occurrence of patient-reported flare-ups through week 28 (Yes/No)
- Occurrence of clinician-assessed flare-ups through weeks 28 and 56 (Yes/No)
- Number of patient-reported flare-ups through weeks 28 and 56
- Change from baseline in joint function assessment by physician to week 28 and week 56 by the CAJIS
- Change from baseline in pulmonary function as assessed by spirometry at week 28 and week 56
- Change from baseline in disease severity to week 28 and week 56 by the PGIS
- Change since the start of the study in disease severity to week 28 and week 56 by the PGIC
- Change since the start of the study in disease severity to week 28 and week 56 by the CGIC

For patients continuing extended treatment, additional other secondary efficacy endpoints are:

- Number of new HO lesions at week 84
- Occurrence of new HO lesions at week 84 (Yes/No)
- Total volume of new HO lesions at week 84
- Number of clinician-assessed flare-ups through week 84
- Occurrence of clinician-assessed flare-ups through week 84 (Yes/No)

Exploratory Endpoints

The exploratory endpoints are:

- [redacted]
- [redacted]

7.2. Analysis of Efficacy Data

7.2.1. Analysis of Primary Endpoint

Estimand Framework for the Primary Endpoint

The estimand for the primary efficacy objective to assess the effect of garetosmab versus placebo on the formation of new HO lesions from baseline to week 56, as determined by low dose CT, is defined below:

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Population	Patients with FOP
Endpoint	Number of new HO lesions at week 56
Treatments	Garetosmab at each dose level vs placebo
Handling of intercurrent event	The intercurrent events of interest include: • Premature discontinuation of study treatment: Treatment policy strategy will be used to address these intercurrent events, specifically, the value for the endpoint is used regardless of adherence to study treatment. • [redacted]
Population-level summary and treatment comparison	The rate of new HO lesion formation, defined as the mean number of new HO lesions formed per year during the 56 weeks of DBTP, will be the population-level summary measure of treatment effect. The comparison of treatment effect will be quantified by the rate ratio, defined as the ratio of the rates of new HO lesion formation.

In primary efficacy analysis, the primary efficacy endpoint will be compared between each dose of garetosmab and placebo for patients in the FAS. Number of new HO lesions at week 56 will be analyzed using a negative binomial regression model. The analysis model will include the fixed categorical effect of treatment groups (garetosmab 10 mg/kg IV Q4W [high dose], garetosmab 3 mg/kg IV Q4W [low dose] and placebo). The ratio of rates for new HO lesion formation will be tested for each garetosmab treatment group versus placebo at the 2-sided 0.05 alpha level. The estimated rate ratio together with the 95% confidence interval (CI) will be provided to compare the treatment groups. Estimated rates of new lesion formation will also be provided with associated 95% CI for each treatment group. The analysis will be implemented using [redacted] of SAS software package version 9.4 or later.

[redacted]

Handling of Missing Data

The missing values in new HO lesions (excluding missing data due to death) will be imputed using a fully conditional specification (FCS) with the predictive mean matching (PMM) method based on the observed data from the given treatment group. The imputation process will be carried out in two stages.

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- First Stage: Week 28Focus: Missing values at week 28
  - Imputation Model: Includes treatment group and baseline CAJIS total score (≤12, >12).
- Second Stage: Week 56
  - Focus: Missing values at week 56
  - Imputation Model: Includes treatment group, baseline CAJIS total score (≤12, >12), and the count of new HO lesions at week 28Since the abnormal bone formed at an earlier timepoint is likely to be apparent on later CT scans, the imputed datasets will restrict the imputed values at week 28 not to exceed the number of new lesions on the later scan. Thus, the following steps will be implemented after imputations.
- For patients with a missing CT scan at week 28 but a CT scan at week 56 that is not missing, if the imputed value for week 28 is greater than the value at week 56, the imputed value for week 28 will be replaced with the value from week 56.
- For patients with a missing CT scan at week 56 but a CT scan at week 28 that is not missing, if the imputed value for week 56 is less than the value at week 28, the imputed value for week 56 will be replaced with the value from week 28.
- If both the week 28 and week 56 CT scans are missing for a patient, and the imputed value at week 56 is smaller than that at week 28, then the imputed value at week 56 will be adjusted to match the imputed value at week 28.

[redacted]

A total of 100 imputed datasets will be generated and the number of closest observations to be used will be 3 in the PMM. The negative binomial regression model described previously will be applied to each of the imputed dataset. The estimates from the model will then be combined using Rubin's formulae to obtain the final estimate of log(rate ratio), 95% CI and the associated p-value. The rate ratio and 95% CI will be derived by taking the exponential of these estimates.

7.2.1.1. Sensitivity Analysis

Sensitivity analyses are planned to assess an alternative method to impute missing data. With respect to the missing data handling of the number of new HO lesions, sensitivity analyses will be performed to confirm robustness of the conclusion drawn based on the main model for primary analysis.

Single Imputation

Missing data for new HO lesions at week 56 will be imputed using the median number of new lesions from patients with observed new lesions in the given treatment group.

Multiple Imputation Using Placebo Washout Method

Missing data at week 56 will be imputed 100 times based on the observed data from the placebo group only. Imputation will be done using FCS with PMM method including baseline CAJIS

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total score (≤12, >12) and number of new HO lesions at week 28. If the imputed value is less than the last observed value, the last observed value will be used.

Tipping Point Analysis

If the primary analysis is significant, a tipping point analysis will be conducted as follows:

- Missing data at week 56 will be imputed 100 times using FCS with PMM method, as specified in Section 7.2.1.
- A series of analyses will be performed by varying the number of new HO lesions for patients with missing data within each treatment group. For example, the number of new HO lesions from multiple imputations in the placebo group will be reduced by a number ranging from 0 to 5, with any negative imputed number being replaced with 0. Conversely, the number of new HO lesions from multiple imputations in the garetosmab group will be increased by a number ranging from 0 to 5.
- For each combination, each of the 100 imputed datasets will be analyzed using the negative binomial regression model for the primary analysis.
- A "tipping point" will be identified when the result is no longer statistically significant (i.e., p-value > 0.05).

Death Considered as the Worst Outcome

The intercurrent event (ICE) of death will be considered as the worst outcome and imputed using the worst value among all patients. Missing data at week 56 will be imputed 100 times using FCS with PMM method, as specified in Section 7.2.1.

7.2.1.2. Supportive Analysis

Missing values for new HO lesions at week 56 will not be imputed. Instead, each patient's last available value prior to week 56 will be used. Patients with missing values at both week 28 and week 56 will be excluded.

7.2.1.3. Subgroup Analyses

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary and key secondary efficacy endpoints using descriptive statistics.

Subgroups to be considered are listed as follow:

- Sex (Male, Female)
- Age (<30, ≥30)
- Randomization stratification factor: Baseline CAJIS total score (≤12, >12)
- Randomization stratification factor: Previous participation in LUMINA-1 (Yes, No)
- Region (Japan, China [excluding patients from Hong Kong], EU, Other [including patients from Hong Kong and US])
- Race (White, Other)

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- Ethnicity (Hispanic or Latino, Not Hispanic or Latino or Not Reported)

7.2.2. Analyses of Secondary Endpoints

7.2.2.1. Analysis of Key Secondary Endpoints

The estimands for the key secondary objectives are provided below:

- To assess the effect of garetosmab (10 mg/kg and 3 mg/kg) versus placebo on the number per patient of clinician-assessed flare-up episodes to week 56
- To assess the effect of garetosmab (10 mg/kg and 3 mg/kg) versus placebo on the proportion of patients with new HO lesions at week 56
- To assess the effect of garetosmab (10 mg/kg and 3 mg/kg) versus placebo on volume of new HO lesions at week 56
- To assess the effect of garetosmab (10 mg/kg and 3 mg/kg) versus placebo on the proportion on the occurrence of patient-reported flare-up episodes through week 56

Population	Patients with FOP
Endpoint	• Number of clinician-assessed flare-ups through week 56 • Occurrence of new HO lesions at week 56 (Yes/No) • Total volume of new HO lesions at week 56 • Occurrence of patient-reported flare-ups through week 56 (Yes/No)
Treatments	Garetosmab at each dose level vs placebo
Handling of intercurrent event	The intercurrent events of interest include: • Premature discontinuation of study treatment: Treatment policy strategy will be used to address these intercurrent events, specifically, the value for the endpoint is used regardless of adherence to study treatment. • Death [redacted] [redacted]

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	[redacted]
Population-level summary and treatment comparison	• Number of clinician-assessed flare-ups through week 56: The rate of clinician-assessed flare-ups, defined as the mean number of new clinician-assessed flare-ups per year during the 56 weeks of DBTP, will be the population-level summary measure of treatment effect. The comparison of treatment effect will be quantified by the rate ratio, defined as the ratio of the rates of clinician-assessed flare-ups. • Occurrence of new HO lesions at week 56 (Yes/No): Difference in the proportion of patients with new HO lesions between garetosmab dose group and placebo • Total volume of new HO lesions at week 56: Difference in mean in total volume of new HO lesions between garetosmab dose group and placebo • Occurrence of patient-reported flare-ups through week 56 (Yes/No): Difference in the proportion of patients with patient-reported flare-ups between garetosmab dose group and placebo

The key secondary endpoint of the number of clinician-assessed flare-ups through week 56 collected via eCRF clinician-assessed flare-up form will be analyzed using a negative binomial regression model for the comparisons of high dose versus placebo and low dose versus placebo. The analysis model will include the fixed categorical effect of treatment group, with logarithm of the duration of period within which flare-ups are assessed being an offset variable. The p-values for the 2-sided hypothesis testing on rate ratios of clinician-assessed flare-ups (10mg/kg versus placebo and 3mg/kg versus placebo) will be provided together with the estimated rate ratios and the associated 95% CI. Rates of clinician-assessed flare-ups will also be provided with associated 95% CI for each treatment group.

[redacted]

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The key secondary endpoints including occurrence of new HO lesions at week 56 (Yes/No) and occurrence of patient-reported flare-ups through week 56 (Yes/No) will be analyzed using Barnard's exact test. The proportions of patients between each garetosmab dose group and placebo will be compared. The proportions and the associated 95% Wald CIs for each treatment group, as well as the proportion difference between each garetosmab dose group and placebo, along with its corresponding 95% Miettinen-Nurminen CIs, will be reported.

The key secondary endpoint of total volume of new HO lesions at week 56 will be analyzed using the Wilcoxon rank-sum test. This test will be used to calculate the p-value for comparing the difference between each garetosmab treatment group and placebo. The 95% CI for the difference of mean total volume will be determined using the bootstrap method.

The handling of missing data and sensitivity analysis for the key secondary endpoints are provided below:

Key Secondary Endpoints	**Handling of Missing Data**	**Sensitivity Analysis**
Number of clinician-assessed flare-ups through week 56	The missing data is accounted for by adjusting for the actual duration of DBTP in the negative binomial regression model.	<u>Single Imputation</u> Negative binomial regression model includes the fixed categorical effect of treatment group only will be used for the treatment comparison. For patients who discontinued from the study prior to week 56, missing values for number of flare-ups through week 56 will be imputed using the median number of flare-ups from patients who did not discontinue from the study prior to week 56 in the given treatment group. If the imputed value is less than the last observed value, the last observed value will be used. <u>Multiple Imputation Using Placebo Washout Method</u> For patients who discontinued from the study prior to week 56, missing values for number of flare-ups through week 56 will be imputed 100 times based on the observed data from the placebo group only. Imputation will be done using FCS with PMM method including baseline CAJIS total score (≤12, >12) and number of flare-ups

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		through week 28. If the imputed value is less than the last observed value, the last observed value will be used. Each of the 100 imputed datasets will be analyzed using a negative binomial regression model includes the fixed categorical effect of treatment group only. <u>Death Considered as the Worst Outcome</u> The intercurrent event (ICE) of death will be considered as the worst outcome and imputed using the worst value among all patients. The negative binomial regression model from the primary analysis will be used for comparing treatments.
Occurrence of new HO lesions at week 56 (Yes/No)	Missing data will be handled through the imputed number of new HO lesions based on the observed data from the given treatment group. A total of 100 imputed datasets will be generated. If the imputed number of lesions for the primary efficacy analysis is greater than zero, occurrence of new HO lesions is Yes; otherwise, it is No.	<u>Single Imputation</u> Patients with missing values for new HO lesions will be considered having new lesions. Barnard's exact test will be used for the treatment comparison. <u>Multiple Imputation Using Placebo Washout Method</u> Missing data will be handled through the imputed number of new HO lesions based on the observed data from the placebo group only. A total of 100 imputed datasets will be generated. If the imputed number of lesions for the primary efficacy analysis is greater than zero, occurrence of new HO lesions will be indicated as "Yes"; otherwise, it will be indicated as "No".

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Total volume of new HO lesions at week 56	Missing data will be handled using the imputed status of occurrence of new HO lesions based on the observed data from the given treatment group. A total of 100 imputed datasets will be generated. If a patient has a new lesion, the imputed total volume is the median total volume from patients with new lesions in the given treatment group. Otherwise, it is imputed as 0.	Single Imputation Consider patients with missing data having new lesions. Total volume of new HO lesions will be imputed by the median total volume from patients with new lesions in the given treatment group. Wilcoxon rank-sum test will be used for the treatment comparison. Multiple Imputation Using Placebo Washout Method Missing data will be handled using the imputed status of occurrence of new HO lesions based on the observed data from the placebo group only. A total of 100 imputed datasets will be generated. If a patient has a new lesion, the imputed total volume is the median total volume from patients with new lesions in the placebo group only. Otherwise, it is imputed as 0. Death Considered as the Worst Outcome The intercurrent event (ICE) of death will be considered as the worst outcome and imputed using the worst value among all patients. Missing data will be handled in the same manner as in the primary analysis.
Occurrence of patient-reported flare-ups through week 56 (Yes/No)	The occurrence of patient-reported flare-ups will be determined by the flare-up data collected in diary.	Single Imputation Patients who discontinue from the study before week 56 will be assumed to have flare-ups. Barnard's exact test will be used for the treatment comparison. Multiple Imputation Using Placebo Washout Method For patients who discontinued from the study prior to week 56, missing values for number of flare-ups through week 56 will be imputed 100 times based on the observed data from the placebo

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		group only. Imputation will be done using FCS with PMM method including baseline CAJIS total score (≤12, >12) and number of flare-ups through week 28. When the imputed value is less than the last observed value, the last observed value will be used. If the imputed number of flare-ups is greater than zero, occurrence of flare-ups will be indicated as "Yes"; otherwise, it will be indicated as "No". This analysis will not be conducted if all patients who discontinued the study before week 56 experienced flare-ups prior to discontinuation.

7.2.2.2. Analysis of Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints will be analyzed based on the FAS. The analysis methods and missing data handling are provided in the following table. The endpoints will be compared for 10 mg/kg versus placebo and 3 mg/kg versus placebo. Handling of the intercurrent events will be consistent with that used for the primary and key secondary endpoints.

Endpoints	Analysis Methods
• Number of new HO lesions at week 28	The model for the primary analysis will be used. <u>Handling of Missing Data</u> The missing values in new HO lesions will be imputed using a fully conditional specification (FCS) with the predictive mean matching (PMM) method. Details are provided in Section 7.2.1.
• Number of clinician-assessed flare-ups through week 28 • Number of patient-reported flare-ups through week 28 • Number of patient-reported flare-ups through week 56	The analysis model for the similar corresponding key secondary endpoint will be used. <u>Handling of Missing Data</u> The missing data is accounted for by adjusting the actual duration of DBTP in the negative binomial regression model.

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Endpoints	Analysis Methods
• Occurrence of new HO lesions at week 28 (Yes/No)	The proportions of patients between garetosmab dose group and placebo will be compared using Barnard's exact test. The proportions and the associated 95% Wald CIs for each treatment group, as well as the proportion difference between each garetosmab dose group and placebo, along with its corresponding 95% Miettinen-Nurminen CIs, will be reported. Handling of Missing Data Missing data will be handled through the imputed number of new HO lesions. The imputed number of lesions will determine whether that patient will be classified as a responder (Yes) or non-responder (No).
• Total volume of new HO lesions at week 28	The Wilcoxon rank-sum test will be employed to calculate the p-value for the comparison of the difference between each garetosmab treatment group and placebo. The 95% CI for the difference of mean total volume will be determined using the bootstrap method. Handling of Missing Data Missing data will be handled using the imputed status of occurrence of new HO lesions. If a patient has a new lesion, the imputed total volume is the median total volume from patients with new lesions in the given treatment group. Otherwise, it is imputed as 0.
• Occurrence of patient-reported flare-ups through week 28 (Yes/No) • Occurrence of clinician-assessed flare-ups through week 28 (Yes/No) • Occurrence of clinician-assessed flare-ups through week 56 (Yes/No)	The proportions of patients between each garetosmab dose group and placebo will be compared using Barnard's exact test. The proportions and the associated 95% Wald CIs for each treatment group, as well as the proportion difference between each garetosmab dose group and placebo, along with its corresponding 95% Miettinen-Nurminen CIs, will be reported. The occurrence of clinician-assessed/patient-reported flare-ups will be determined by the observed flare-up data (No imputation for the missing visits).
• Change from baseline in joint function assessment	The change from baseline values will be analyzed by the analysis of covariance (ANCOVA) model. The ANCOVA

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Endpoints	Analysis Methods
by physician to week 28 by the CAJIS • Change from baseline in joint function assessment by physician to week 56 by the CAJIS • Change from baseline in disease severity to week 28 by the PGIS • Change from baseline in disease severity to week 56 by the PGIS	model will include treatment as fixed effect and the baseline value as continuous covariate. <u>Handling of Missing Data</u> The missing data at weeks 28 or 56 will be imputed by Last Observation Carried Forward (LOCF) approach.
• Change from baseline in pulmonary function as assessed by spirometry at week 28 • Change from baseline in pulmonary function as assessed by spirometry at week 56	The change from baseline values will be analyzed by the analysis of covariance (ANCOVA) model, based on the completers who had spirometry assessments at both baseline and week 28 / week 56. The ANCOVA model will include treatment as fixed effect, and the baseline value as continuous covariate. Note: Pulmonary function is assessed only in patients capable of undergoing the procedure.
• Change since the start of the study in disease severity to week 28 by the CGIC • Change since the start of the study in disease severity to week 56 by the CGIC • Change since the start of the study in disease severity to week 28 by the PGIC • Change since the start of the study in disease severity to week 56 by the PGIC	The change since the start of the study in disease severity by the PGIC will be analyzed by the analysis of variance (ANOVA) model. The ANOVA model will include treatment as fixed effect. <u>Handling of Missing Data</u> The missing data at weeks 28 or 56 will be imputed by Last Observation Carried Forward (LOCF) approach.

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7.2.2.3. Analysis of Additional Other Secondary Efficacy Endpoints

For patients continuing extended treatment, additional other secondary efficacy endpoints are:

- Number of new HO lesions at week 84
- Occurrence of new HO lesions at week 84 (Yes/No)
- Total volume of new HO lesions at week 84
- Number of clinician-assessed flare-ups through week 84
- Occurrence of clinician-assessed flare-ups through week 84 (Yes/No)

During the ETP, efficacy variables will be explored through descriptive statistics at each scheduled visit for each study treatment received in the DBTP (ie, garetosmab 2 doses, placebo). Treatment comparison will also be explored for patients who have observed data at week 84.

7.2.2.4. Analysis of Exploratory Endpoints

Duration and severity level of patient-reported new flare-up will be summarized descriptively in the FAS population.

[redacted]

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8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

The overall Type I error is controlled at two-sided 5% for each comparison of garetosmab doses with placebo to balance the statistical considerations while allowing robust evaluation of treatment effects for each dose.

In order to control the two-sided 5% type-I error for each garetosmab treatment group compared to placebo with respect to the primary and key secondary efficacy endpoints, a separate prespecified hierarchical inferential approach will be used for each dose. Statistical significance of primary efficacy analysis is required in the respective garetosmab treatment group compared to placebo before proceeding to the first key secondary efficacy analysis at the two-sided 0.05 alpha level. Inferential conclusions about successive secondary analysis require statistical significance of the prior analysis within the hierarchy. The hierarchy testing sequence is provided below, with each garetosmab treatment group compared to placebo independently. This fixed hierarchical approach will ensure a strong control of the type-I error rate at the two-sided 0.05 level for each garetosmab treatment group compared to placebo. No further adjustments will be made for other secondary analysis not in the hierarchy, for which p-values will be provided for descriptive purposes only.

Table 1: Hierarchical Order for Each garetosmab dose

	Endpoints	Testing Order
Primary Endpoint	Number of new HO lesions at week 56	1
Key Secondary Endpoints	Number of clinician-assessed flare-ups through week 56	2
	Occurrence of new HO lesions at week 56 (Yes/No)	3
	Total volume of new HO lesions at week 56	4
	Occurrence of patient-reported flare-ups through week 56 (Yes/No)	5
Other Secondary Endpoints	Occurrence of clinician-assessed flare-ups through week 56 (Yes/No)	6
	Number of patient-reported flare-ups through week 56	7
	Change from baseline in joint function assessment by physician to week 56 by the CAJIS	8
	Change from baseline in disease severity to week 56 by the PGIS	9
	Change since the start of the study in disease severity to week 56 by the PGIC	10
	Change since the start of the study in disease severity to week 56 by the CGIC	11
	Number of new HO lesions at week 28	12
	Number of clinician-assessed flare-ups through week 28	13
	Occurrence of new HO lesions at week 28 (Yes/No)	14
	Total volume of new HO lesions at week 28	15

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	Occurrence of patient-reported flare-ups through week 28 (Yes/No)	16
	Occurrence of clinician-assessed flare-ups through week 28 (Yes/No)	17
	Number of patient-reported flare-ups through week 28	18
	Change from baseline in joint function assessment by physician to week 28 by the CAJIS	19
	Change from baseline in disease severity to week 28 by the PGIS	20
	Change since the start of the study in disease severity to week 28 by the PGIC	21
	Change since the start of the study in disease severity to week 28 by the CGIC	22

8.1. US-Specific Testing Strategy

The testing sequence for the primary and key secondary efficacy endpoints is as follows:

Step 1: Test garetosmab 10 mg/kg (high dose) vs. placebo on the primary endpoint using a two-sided alpha level of 0.05.

Step 2: If garetosmab 10 mg/kg is shown to be superior to placebo with statistical significance on the primary endpoint, then perform a comparison to placebo using a two-sided alpha level of 0.05, for each dose separately based on the prespecified testing order of the endpoints outlined in Table 1.

The efficacy of garetosmab 3 mg/kg (low dose) will be assessed only after the efficacy of the 10 mg/kg dose is established on the primary endpoint. With this approach, the overall Type I error is controlled at a two-sided alpha level of 0.05 for the primary endpoint. Considering that this is a rare disease setting, this strategy allows reasonable flexibility in testing clinically important secondary endpoints and the efficacy of the low dose, while still maintaining strong control over the overall Type I error on the primary endpoint across the two doses.

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9. SUMMARY OF EXPOSURE DATA

9.1. Study Drug Exposure and Compliance

Treatment Exposure

The following treatment exposure data in DBTP will be summarized by treatment group:

- Duration of study drug exposure in weeks defined as: (date of last DBTP study drug administration - date of first DBTP study drug administration + 28 days)/7
- Total number of study treatment infusions received during DBTP by patient

The following treatment exposure data over the entire study will be summarized by treatment group:

- Duration of study drug exposure in weeks defined as: (date of last study drug administration - date of first study drug administration + 28 days)/7
- Total number of study treatment infusions received over the entire study by patient

The durations of study treatment exposure (DBTP and the entire study), measured in weeks, will be summarized for each treatment group using the number of patients, mean, SD, median, Q1, Q3, minimum, and maximum.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories as well:

- DBTP: ≥ 4 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 20 weeks, ≥ 24 weeks, ≥ 28 weeks, ≥ 32 weeks, ≥ 36 weeks, ≥ 40 weeks, ≥ 44 weeks, ≥ 48 weeks, ≥ 52 weeks, ≥ 56 weeks
- The entire study: ≥ 28 weeks, ≥ 56 weeks, ≥ 64 weeks, ≥ 72 weeks, ≥ 84 weeks, ≥ 92 weeks, ≥ 104 weeks, ≥ 112 weeks

The number of study treatment infusions (DBTP and the entire study) will be summarized for each treatment group using the number of patients, mean, SD, median, Q1, Q3, minimum, and maximum. In addition, the number of study treatment infusions will be summarized categorically by patient counts and percentages.

Treatment Compliance

For the DBTP, compliance with protocol-defined investigational product will be calculated as follows:

Treatment compliance = (Number of infusions of study drug during exposure period)/(Number of planned infusions of study drug during exposure period on or before the time that the patient discontinues from the study) x 100%.

Treatment compliance will be descriptively summarized for each treatment group. In addition, the number (%) of patients with treatment compliance <90% and ≥90% will be presented.

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9.2. Prior and Concomitant Medications

Medications will be recorded from the time of informed consent to final study visit and will be coded using WHO Drug Dictionary (WHODD). This includes medications that were started before the study and are ongoing during the study. The prior and concomitant medications are defined as below:

- Prior medications are defined as any medications for which the stop date is before the date of the first study drug administration.
- Concomitant medications are defined as any medications that are administered to the patients following the dose of study drug through the final study visit.

Number and proportion of subjects taking prior/concomitant medications will be summarized by treatment group and overall patients based on the FAS, sorted by decreasing frequency of ATC Level 2 and PT of the overall group.

9.3. Prior and Concomitant Procedures

Procedures will be recorded from the day of informed consent to final study visit and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The prior and concomitant procedures are defined as below:

- Prior procedures are defined as any procedures performed prior to administration of the first dose of study drug.
- Concomitant procedures are defined as any procedures performed following the dose of study drug through the final study visit.

Number and proportion of subjects taking prior/concomitant procedures will be summarized by treatment group and overall patients based on the FAS, sorted by decreasing frequency of SOC and PT of the overall group.

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10. ANALYSIS OF SAFETY DATA

Safety and tolerability will be descriptively summarized in SAF by treatment group (placebo, garetosmab 3 mg/kg IV, garetosmab 10 mg/kg IV, and any garetosmab), including AEs, clinical laboratory variables, vital signs, 12-lead ECG, and platelet flow cytometry variables.

Thresholds for treatment-emergent potentially clinically significant values (PCSV) in laboratory variables, vital signs, and ECG are defined in Appendix 14.3.

All safety analyses will be performed using the following common rule:

- The baseline value is defined as the last available value before the first dose of DBTP study treatment.
- PCSV criteria specified in Appendix 14.3 for lab oratory paraemeters, vital signs and ECG will determine which subjects had at least 1 PCSV during the respective study periods (DBTP and overall study period) taking into account all evaluations including unscheduled or repeated evaluations.
- All unscheduled measurements will be assigned to respective analysis windows defined in Appendix 14.4 in order to provide an assessment for the screening/baseline visit through post-baseline visit time points.

10.1. Adverse Events

All new or worsening adverse events (AEs) occurring between signing of the ICF and the end of the study will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The definitions of AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs) are provided in Sections 10.2.1-10.2.3 of the protocol. Treatment-emergent adverse events (TEAEs) are AEs that developed or worsened or became serious during the corresponding observation period defined below.

The following observation periods are:

1. The DBTP TEAE observation period is defined from the day of the first dose of double-blind study treatment to the day of week 56 visit for those patients who complete week 56, or up to their last dose date + 28 days for those patients who discontinue the study treatment before week 56.
2. The on-study TEAE period is defined from the day of the first study treatment administration to the end of the study.

The number and percentage of patients with TEAEs will be summarized for each observation period. Summaries will include:

- Overall TEAE summary including patients with any:
  - TEAE
  - Treatment-emergent SAE (TE-SAE)
  - Severe TEAE
  - Treatment-related TEAE

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  - TEAE leading to death
  - TEAE leading to study treatment discontinuation
- TEAEs by SOC/PT
- TEAEs by PT
- TEAEs by SOC/PT and maximum severity
- Treatment-related TEAEs by SOC/PT
- TE-SAEs by SOC/PT
- TEAEs leading to permanent treatment discontinuation by SOC/PT
- TEAEs leading to death by SOC/PT

10.1.1. Adverse Events of Special Interest

Below are adverse events of special interest (AESI) categories collected from AE eCRF form for this study.

- Epididymitis, Orchitis, hydrocele, scrotum pain and/or scrotum swelling
- Moderate to severe episodes of spontaneous non-traumatic bleeding
- Moderate epistaxis (defined as any episode lasting longer than 30 minutes or requiring professional medical intervention)
- Severe epistaxis (based on definition of a severe AE as per protocol)
- Skin infection/abscess that requires referral to specialist for treatment

Overview of TE-AESIs and TE-AESIs by Primary SOC, and PT will be provided.

In addition, the following safety events will be analyzed.

- Male reproductive organ events: These events will be identified through AESI category of “Epididymitis, Orchitis, hydrocele, scrotum pain and/or scrotum swelling” as collected from AE eCRF form.
- Bleeding events: These events will be identified through the Standardized MedDRA Queries, SMQ(n) Haemorrhage.
- Epistaxis: All events with PT of "Epistaxis" will be included.
- Skin infections: These events will be identified through the following criteria: 1) TEAEs with PTs that contain the word "abscess“, “folliculitis”, “cellulitis”, “furuncle”, “rash pustular”, and “carbuncle”; OR 2) HLT of “Acnes”.
- Infusion reactions: These events will be identified through the question “Is this Adverse Event an infusion related reaction?” from AE eCRF form.
- Allergic events: These events will be defined by using SMQ “hypersensitivity” (broad) OR PT of “idiopathic angioedema”.

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10.2. Laboratory Parameters

Clinical laboratory tests specified in Section 9.2.4.9 of the protocol will be collected at time points according to the schedule in Appendix 14.2 and summarized by the treatment periods defined in Section 11.4.5.2 of the protocol.

Laboratory measurements will be reported using both conventional units and standard international units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory results and change from baseline values by visit
- Shift tables based on baseline normal/abnormal may be used to present the results for parameters of interest
- The incidence of patients with PCSVs at any time during the respective study periods (DBTP and on-treatment period) will be summarized regardless of the baseline level, and again according to the following baseline status:
  - Normal/missing

10.3. Vital Signs

The following vital signs parameters will be recorded and summarized according to the Schedule Events in Appendix 14.2 and summarized by the treatment periods defined in Section 11.4.5.2 of the protocol.

- Temperature
- Blood pressure
- Pulse rate
- Respiration rate

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable results and change from baseline values by visit
- The incidence of patients with PCSVs at any time during the respective study periods (DBTP and on-treatment period)

10.4. Electrocardiography (ECG)

The following standard 12-lead ECG parameters will be recorded and analyzed summarized according to the Schedule Events in Appendix 14.2 and summarized by the treatment periods defined in Section 11.4.5.2 of the protocol.

- Ventricular rate
- PR interval
- QRS interval
- RR interval

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- QT interval
- QTc Fridericia [QTcF]
- QTc Bazett [QTcB]
- ECG status: normal, abnormal not clinically significant or abnormal clinical significant.

Summaries of 12-lead ECG parameters by treatment group will include:

- Descriptive statistics of ECG parameter results and change from baseline values by visit
- The incidence of patients with PCSVs at any time during the respective study periods (DBTP and on-treatment period)
- ECG status (i.e. normal, abnormal) summarized over time by a shift table

10.5. Platelet Flow Cytometry Parameters

The percentage of positive events from baseline through week 56 will be summarized, where a positive event is defined as a platelet determined to be either P-selectin positive or procaspase-activating compound 1 (PAC-1) positive (activated glycoprotein IIb/IIIa [GPIIb/IIIa]) via platelet flow cytometry.

10.6. Immunogenicity Data

10.6.1. Immunogenicity Variables

The immunologenicity variables include:

- ADA status (positive or negative), titer, and time-point/visit

Serum samples for ADA will be collected at the clinical visits as specified in Appendix 14.2. Samples positive in the ADA assay will be further characterized for ADA titers.

10.6.2. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 10.5.1 will be summarized by ADA status, ADA category and maximum titer category observed in patients in the ADA analysis set. For samples confirmed as drug-specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value.
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive patient is classified as:

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- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥ 9-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
  - Transient - Not persistent or indeterminate, regardless of any missing samples

The maximum titer category of each patient is classified as:

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of patients with negative ADA
- Number (n) and percent (%) of patients with pre-existing ADA
- Number (n) and percent (%) of patients with treatment-emergent ADA
  - Number (n) and percent (%) of patients with persistent treatment-emergent ADA positive
  - Number (n) and percent (%) of patients with indeterminate treatment-emergent ADA positive
  - Number (n) and percent (%) of patients with transient treatment-emergent ADA positive
- Number (n) and percent (%) of patients with treatment-boosted ADA positive

10.6.3. Association of Immunogenicity with Exposure, Safety and Efficacy

10.6.3.1. Immunogenicity and Exposure

Potential association between immunogenicity and systemic exposure to REGN2477 will be explored by treatment groups. Plots of individual REGN2477 concentration-time profiles may be provided to examine the potential impact of ADA status, ADA category and maximum titer category on these profiles.

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10.6.3.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA status
  - Treatment-emergent and treatment-boosted
  - Negative and pre-existing
- Maximum titer category
  - High
  - Moderate
  - Low

10.7. Pharmacokinetic Data

Analysis of pharmacokinetics drug concentration data will include Summary of functional REGN2477 and will be presented by nominal time point (i.e., the time points specified in the protocol) using the pharmacokinetic analysis set. Plots of drug concentration will be presented over time (linear and log scales). When the scale is linear,concentrations below the lower limit of quantification (LLOQ) will be set to zero. In the log-scaled figures, concentrations below the LLOQ will be imputed as LLOQ/2.

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11. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

11.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. The following rules specify the determination by both date/time information:

1. For the AE, vital signs, lab (including biomarker), drug concentration and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first infusion date and time.
2. For other data except AE, vital signs, lab (including biomarker), drug concentration or ADA, only date of the measurement will be used to determine baseline by comparing with the first infusion date.

For the rescreened patients, all data from the same patient will be used to derive baseline regardless if the data is from the screen-failure subject ID or randomized subject ID.

11.2. Data Convention

For the laboratory safety variables and biomarker data, if the data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

11.3. Data for Non-Efficacy Endpoints

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Missing/incomplete dates

Every effort will be made to collect the start dates of all AEs and concomitant medications/procedures. However, in the case the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the first dose of study medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the first dose of study medication date, then the start date of the first dose will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAE. If the measurement of relationship of a TEAE to the investigational product is missing, it will be classified as “related” in the frequency tables by relation to the investigational product.

Medication coding

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Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these un-coded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Data analyzed by-visit-analysis will be summarized by the study scheduled visits described in Appendix 14.2. The analysis visit windows will be exclusive so that all available values obtained from unscheduled visits and early termination visit (ETV) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits. The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Day 1 is defined as the first date of study treatment administration and for patients who were randomized but not treated it is defined as the day of randomization.

The analysis windows are defined in Appendix 14.4. In general, the following order will be used to select the record for analysis at given visit:

1. Scheduled visit
2. Early termination (ET) if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ETV are not available

For the multiple measurements of the same test in the same window, the following rules will be used to pick up the analysis value:

- If multiple valid values of a variable within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

11.5. Pooling of Categorical Variables for Statistical Analyses

No categorical variables will be pooled in the analyses.

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12. TECHNICAL DETAILS PERTAINING TO INTERIM ANALYSIS/(ES)

No formal interim analysis is planned.

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13. REFERENCES

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14. APPENDIX

14.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Descriptive Analysis	Sensitivity Analyses
Primary Endpoint						
Number of new HO lesions at week 56	FAS	Comparison of new HO lesion rates between garetosmab 10 mg/kg IV Q4W and placebo, and between garetosmab 3 mg/kg IV Q4W and placebo, separately	Negative binomial regression, or Wilcoxon rank-sum test if negative binomial regression fails	Yes	Yes Subgroups: sex, age, baseline CAJIS total score, previous participation in LUMINA-1, region, race, Ethnicity	Yes
Key Secondary Endpoint						
Number of clinician-assessed flare-ups through week 56	FAS	Comparison of clinician-assessed flare-up rates between garetosmab 10 mg/kg IV Q4W and placebo, and between garetosmab 3 mg/kg IV Q4W and placebo, separately	Negative binomial regression, or Wilcoxon rank-sum test if negative binomial regression fails	No	Yes Subgroups: sex, age, baseline CAJIS total score, previous participation in LUMINA-1, region, race, Ethnicity	Yes
Occurrence of new HO lesions at week 56 (Yes/No) Occurrence of patient-reported flare-ups through week 56 (Yes/No)	FAS	Comparison of the proportions between garetosmab 10 mg/kg IV Q4W and placebo, and between garetosmab 3 mg/kg IV	Barnard's exact test	No	Yes Subgroups: sex, age, baseline CAJIS total score, previous participation in LUMINA-1, region,	Yes

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Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Descriptive Analysis	Sensitivity Analyses
		Q4W and placebo, separately			race, Ethnicity	
Total volume of new HO lesions at week 56	FAS	Comparison of the mean total volumes between garetosmab 10 mg/kg IV Q4W and placebo, and between garetosmab 3 mg/kg IV Q4W and placebo, separately	Wilcoxon rank-sum test	No	Yes Subgroups: sex, age, baseline CAJIS total score, previous participation in LUMINA-1, region, race, Ethnicity	Yes

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14.2. Schedule of Time and Events

Table 2: Schedule of Events: Screening and DBTP (including Early Termination)

	Screening Period	DBTP																Early Termination
Study Procedure[1,2]	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**End of DBTP/V17[3]**	**V**
Week	**-**	**-**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Day	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	
Window (day)	**-**	**1**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-7 to +15 d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	
Screening/Baseline																		
Inclusion/Exclusion[4]	X																	
Informed Consent (optional genomics sub-study)	X																	
Informed Consent (optional FBR sub-study)	X																	
Informed Consent	X																	
Medical/Prior medication/Surgical History[5]	X																	
Demographics	X																	
Body Height[6]	X																	
Confirm clinical FOP diagnosis including document of ACVR1 mutation[7]	X																	
Whole blood for DNA sample for ACVR1 gene sequencing[8]	X																	
Scrotum ultrasound with doppler (males only)	X																	

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	Screening Period	DBTP																Early Termination
Study Procedure[1,2]	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**End of DBTP/V17[3]**	**V**
Week	**-**	**-**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Day	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	
Window (day)	**-**	**1**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-7 to +15 d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	
Blood samples for FSH (to determine post-menopausal status, if applicable)	X																	
Blood sample for HbA1c	X																	
Randomization		X																
Treatment																		
Administer Study Drug: all patients[9]		X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Administer Study Drug: patients continuing to Extended Treatment[9]																	X[3]	
Concomitant Medications and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Endpoint Measures																		
Low-dose whole body CT[10,11]	X									X							X[12]	X[13]
Daily FOP Flare-up diary[14]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CAJIS	X									X							X	X
EQ-5D-3L	X									X							X	X
SF-36	X									X							X	X
PGIS	X									X							X	X
PGIC										X							X	X
Patient experience interview																X[15]		X
CGIC										X							X	X
Spirometry (FVC/FEV-1)[16]	X									X							X	X

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	Screening Period	DBTP																Early Termination
Study Procedure[1,2]	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**End of DBTP/V17[3]**	**V**
Week	**-**	**-**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Day	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	
Window (day)	**-**	**1**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-7 to +15 d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	
FOP Clinician-assessed Flare		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety																		
Vital signs[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X									X							X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Menstrual history (female) and confirmation of contraception use (male and female)[18]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ENT consultation[19]	X		follow-up visits as needed[19]															
Laboratory Testing[20]																		
Pregnancy test (WOCBP)	serum[21]	urine		urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	serum
Hematology	X[21]	X		X	X	X	X	X		X			X				X	X
Blood chemistry	X[21]	X		X	X	X	X	X		X			X				X	X
Urinalysis[22]	X	X		X	X	X	X	X		X			X				X	X
Platelet flow cytometry[23]	X	X		X	X	X	X			X			X				X	
Blood sample for Coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time) and fibrinogen	X	X				X				X			X				X	X

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	Screening Period	DBTP																Early Termination
Study Procedure[1,2]	**V1**	**Baseline V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**End of DBTP/V17[3]**	**V**
Week	**-**	**-**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	
Day	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	
Window (day)	**-**	**1**	**±3d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**-7 to +15 d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	
Blood samples for FSH, estradiol, LH for female patients with regular menstrual cycles[24]	X	→																
PK and Immunogenicity Sampling[25]																		
Blood sample for PK/Drug concentration and activin A		X[26]	X	X	X	X	X	X		X		X	X	X	X	X	X	X
Blood sample BMP-9	X		X							X							X	X
Blood sample for ADA sample		X				X				X							X	X
Biomarkers																		
Blood sample for biomarker samples of bone and cartilage		X		X				X				X					X	
Blood sample for biomarker samples of inflammatory markers		X		X				X				X					X	
Future Biomedical Research																		
Research biomarker serum for future use (optional)[27]		X		X		X		X						X			X	
Research biomarker plasma for future use (optional)[27]		X		X		X		X						X			X	
Pharmacogenomics																		
Whole blood DNA samples (optional)[27]		X																

ACVR1= Type I activin A receptor; ADA=Antidrug antibody; BMP-9=Bone morphogenic protein 9; CAJIS= Cumulative Analog Joint Involvement Scale; CGIC=Clinician's Global Impression of Change; CT= Computed tomography; d=Day; DBTP=Double-Blind Treatment Period; DNA=Deoxyribonucleic acid;

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ENT=Ear, nose, and throat; EOS=Endo f study; EQ-5D-3L= EuroQol 5 dimensions questionnaire with a 3-level scale; FBR=Future biomedical research; FEV1= Forced expiratory volume in 1 second; FOP= Fibrodysplasia ossificans progressiva; FSH=Follicle-stimulating hormone; FVC= Forced vital capacity; HbA1c=Hemoglobin A1c; INR=International normalized ratio; LH=Luteinizing hormone; PK=Pharmacokinetic; PGIC=Patient's Global Impression of Change; PGIS=Patient's Global Impression of Severity; SF-36=Short-Form 36; V=Visit; WOCBP=women of childbearing potential.

14.2.1. Footnotes for Schedule of Events for Table 2

1. Procedures other than those associated with imaging procedures may be conducted by trained study staff at or near patients' residences (ie, at-home visits).
2. During the study, study procedures within each visit may be conducted on different days, within the stated visit window. If conducted on the same day, vital signs and ECG will be conducted before blood sampling, and blood samples will be collected before CT procedure.
3. At the week 56 visit, patients will have a discussion with the study doctor and choose to continue blinded treatment and enter the ETP or to stop treatment, become unblinded, and enter the Observation Period. For patients that will enter the ETP, study drug is administered at visit 17 and refer to Table 3. For patients that will be unblinded, no study drug is administered at visit 17 and refer to Table 5.
4. Patients may be rescreened once for study participation.
5. Medical history footnote: Medical history should include detailed FOP history, prior medication and surgery for treatment of FOP, history of madarosis, acne, epistaxis, infections, and abscesses and previous participation in LUMINA-1 study
6. Depending upon the level of musculoskeletal compromise for a patient, the measurement of the patient's height may not be precise or sometimes not possible to be assessed.
7. Documentation of ACVR1 genotype, including classic [R206H] or different ACVR1 mutations, should be obtained for the study file for all patients. In China, this data will be collected after Human Genetic Resource Administration of China (HGRAC) approval.
8. All patients will have a whole blood sample collected for ACVR1 gene sequencing, to be analyzed at a central lab. For patients without prior documentation of ACVR1 at screening, the results from this test will be used for documentation. In China, there will be no collection of whole blood samples for ACVR1 sequencing.
9. All patients who receive study drug will be closely monitored after each study drug administration for at least 2 hours.
10. The baseline imaging assessment by low dose CT must be conducted between day-7 to day -1.

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11. Any incidental findings identified through CT scans will be reported to the investigator and medical monitor. The investigator will communicate any findings to the patient.
12. The week 56 CT scan for a patient can be repeated, if needed due to an image quality issue, and if feasible (Section 3.3.7 in the protocol).
13. If the patient had a CT within 12 weeks prior to the early termination visit, then a CT scan is not required.
14. Daily FOP Flare-up diary will be collected as entries in a diary completed by the patient. If the patient is physically unable to or requires assistance to complete the e-diary on their own, caregivers can complete or provide assistance in completion of the e-diary. Caregivers can only physically assist with completion of the e-diary and there is to be no interpretation of patient disease activity on their part. At baseline visit, the FOP Flare-up diary should be completed before study drug administration.
15. Patient experience interviews will be conducted by an external interviewer at week 52, allowable time frame is between week 52 and week 54.
16. Forced vital capacity (FVC) and FEV1, and the ratio of FEV1/FVC, will be determined by spirometry in patients who are able to undergo this procedure.
17. On study day 1 vital signs will be collected pre-dose and post-dose at 2 hours (±30 minutes) after the end of infusion. On subsequent visits, vital signs will be collected prior to dosing.
18. Menstrual history and pregnancy status of WOCBP will be determined at the screening visit. Menstrual events and pregnancy status of WOCBP will be monitored at each visit, except visit 3. A negative result for the pregnancy test must be obtained prior to each study drug administration. For both female and male patients, contraception use will be confirmed.
19. ENT consultation is to be performed during Screening Period. Follow-up visits will be conducted for patients who experience episodes of moderate or severe epistaxis, have more than three episodes of epistaxis, or if deemed necessary by the investigator.
20. In some patients, it may not be possible to obtain venous blood samples for all tests. Serum pregnancy tests and other blood tests for determining eligibility must be obtained. Blood samples for safety labs will be prioritized. Study drug administration will be performed last at that study visit.
21. Blood sample collection for laboratory testing at the screening visit will be collected in a fasted state (after an 8-hour fast). No other blood sample collection will require fasting.
22. A routine urinalysis will be collected in all patients (male and female). In addition, a urinalysis and urine culture will be collected in male patients experiencing an AESI related to the male reproductive system (see Section 10.1.3 in the protocol).

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23. Samples for platelet flow cytometry will be collected at screening, baseline, and at the visits specified (prior to study drug administration) to monitor any changes in platelet activity (eg, clotting capability).
24. Blood samples for FSH, estradiol, and LH will be collected between days 3 to 5 of the menstrual cycle during the Screening Period and during the first 6 months of the study for female patients with regular menstrual cycles. Additional details will be provided in the study reference manual.
25. Samples for PK, ADA, total activin A, and BMP9 analysis must be collected prior to study drug administration. In the event of a suspected SAE such hypersensitivity or anaphylaxis, additional PK and ADA samples may be collected at or near the event.
26. On day 1, a blood sample for drug concentration measurement will also be collected at the end of study drug administration (within 30 minutes after end of infusion). If unable to collect the sample or patients is unwilling to have sample collection from the opposite arm as the initial blood sample, the post administration sample may be omitted.
27. Separate consent is required for participation in the optional Future Biomedical Research and Pharmacogenomics sub-studies. The blood sample for genomic DNA should be collected on day 1 or may be collected at any visit. These optional samples will not be collected in China.

Table 3: Schedule of Events: ETP

	ETP							**Follow-Up Safety Visit**	**Early Termination**
Study Procedure[1,2]	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**End of ETP/V24[4]**	**≥V25**	**V**
Week	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**≥114**	
Day	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**≥798**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
Treatment									
Administer Study Drug: all patients on Extended Treatment[3]	X	X	X	X	X	X			
Administer study drug: patients continuing Extended Treatment[3]							X[4]		
Concomitant Medications and Procedures	X	X	X	X	X	X	X		X
Clinical Endpoint Measures									
Low-dose whole body CT[5]							X		X[6]
CAJIS							X		X
EQ-5D-3L							X		X

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	ETP							Follow-Up Safety Visit	Early Termination
Study Procedure[1,2]	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**End of ETP/V24[4]**	**≥V25**	**V**
Week	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**≥114**	
Day	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**≥798**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
SF-36							X		X
PGIS							X		X
PGIC							X		X
CGIC							X		X
FOP Clinician-assessed Flare	X	X	X	X	X	X	X		X
Safety									
Vital signs[7]	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X
Electrocardiogram							X		X
Adverse events	X	X	X	X	X	X	X	X	X
Menstrual history (female) and confirmation of contraception use (male and female)[8]	X	X	X	X	X	X	X		X
ENT consultation[9]	follow-up visits as needed[9]								
Laboratory Testing[10]									
Pregnancy test (WOCBP)	urine	urine	urine	urine	urine	urine	serum	serum	serum
Hematology			X				X	X	X
Blood chemistry			X				X	X	X
Urinalysis[11]			X				X	X	X
Platelet flow cytometry[12]							X		
Blood sample for Coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time) and fibrinogen			X				X	X	X
PK and Immunogenicity Sampling[13]									
Blood sample for PK/Drug concentration and activin A							X	X	X
Blood sample BMP-9							X	X	X
Blood sample for ADA sample							X	X	X

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	ETP							Follow-Up Safety Visit	Early Termination
Study Procedure[1,2]	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**End of ETP/V24[4]**	**≥V25**	**V**
Week	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**≥114**	
Day	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**≥798**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
Biomarkers									
Blood sample for biomarker samples of bone and cartilage							X	X	
Blood sample for biomarker samples of inflammatory markers							X	X	

ADA=Antidrug antibody; BMP-9=Bone morphogenic protein 9; CAJIS= Cumulative Analog Joint Involvement Scale; CGIC=Clinician's Global Impression of Change; CT= Computed tomography; d=Day; ENT=Ear, nose, and throat; EQ-5D-3L= EuroQol 5 dimensions questionnaire with a 3-level scale; ETP=Extended Treatment Period; FOP= Fibrodysplasia ossificans progressiva; INR=International normalized ratio; PK=Pharmacokinetic; PGIC=Patient's Global Impression of Change; PGIS=Patient's Global Impression of Severity; SF-36=Short-Form 36; V=Visit; WOCBP=women of childbearing potential

14.2.2. Footnotes for Schedule of Events for Table 3

1. Procedures other than those associated with imaging procedures may be conducted by trained study staff at or near patients' residences (ie, at-home visits).
2. During the study, study procedures within each visit may be conducted on different days, within the stated visit window. If conducted on the same day, vital signs and ECG will be conducted before blood sampling, and blood samples will be collected before CT procedure.
3. All patients who receive study drug will be closely monitored after each study drug administration for at least 2 hours.
4. All patients in the ETP will be administered study drug at week 84 (visit 24) and continue Extended Treatment (see Table 4) except the last global patient reaching week 84 who will not receive study drug at week 84 (visit 24) and will continue to the Follow-Up Safety Visit (visit 25 in Table 3).
5. Any incidental findings identified through CT scans will be reported to the investigator and medical monitor. The investigator will communicate any findings to the patient.
6. If the patient had a CT within 12 weeks prior to the early termination visit, then a CT scan is not required.
7. On study day 1 vital signs will be collected pre-dose and post-dose at 2 hours (±30 minutes) after the end of infusion. On subsequent visits, vital signs will be collected prior to dosing.

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8. Menstrual events and pregnancy status of WOCBP will be monitored at each visit, except visit 3. A negative result for the pregnancy test must be obtained prior to each study drug administration. For both female and male patients, contraception use will be confirmed.
9. ENT follow-up visits will be conducted for patients who experience episodes of moderate or severe epistaxis, have more than 3 episodes of epistaxis, or if deemed necessary by the investigator.
10. In some patients, it may not be possible to obtain venous blood samples for all tests. Serum pregnancy tests and other blood tests for determining eligibility must be obtained. Blood samples for safety labs will be prioritized. Study drug administration will be performed last at that study visit.
11. A routine urinalysis will be collected in all patients (male and female). In addition, a urinalysis and urine culture will be collected in male patients experiencing an AESI related to the male reproductive system (see Section 10.1.3 in the protocol).
12. Samples for platelet flow cytometry will be collected at the visits specified (prior to study drug administration) to monitor any changes in platelet activity (eg, clotting capability).
13. Samples for PK, ADA, total activin A, and BMP9 analysis must be collected prior to study drug administration. In the event of a suspected SAE such hypersensitivity or anaphylaxis, additional PK and ADA samples may be collected at or near the event.

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Table 4: Schedule of Events: Continued ETP

	ETP – Continued[1]							Follow-Up Safety Visit	Early Termination
Study Procedure[2,3]	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**End of ETP – Continued/V≥31**	**V≥32**	**V**
Week	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**≥142**	
Day	**617**	**645**	**673**	**701**	**729**	**757**	**785**	**≥994**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
Treatment									
Administer Study Drug[4]	X	X	X	X	X	X			
Concomitant Medications and Procedures	X	X	X	X	X	X	X		X
Clinical Endpoint Measures									
CAJIS						X	X		X
EQ-5D-3L						X	X		X
SF-36						X	X		X
PGIS						X	X		X
PGIC						X	X		X
CGIC						X	X		X
FOP Clinician-assessed Flare	X	X	X	X	X	X	X		X
Safety									
Vital signs[5]	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X		X
Physical examination	X	X	X	X	X	X	X		X
Electrocardiogram							X		X
Adverse events	X	X	X	X	X	X	X	X	X
Menstrual history (female) and confirmation of contraception use (male and female)[6]						X			X
ENT consultation[7]	follow-up visits as needed[7]								
Laboratory Testing[8]									
Pregnancy test (WOCBP)	urine	urine	urine	urine	urine	urine	serum	serum	serum
Hematology						X	X	X	X
Blood chemistry						X	X	X	X
Urinalysis[9]						X	X	X	X
Blood sample for Coagulation parameters (activated partial thromboplastin time, prothrombin time, INR, thrombin time) and fibrinogen						X	X	X	X

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	ETP – Continued[1]							Follow-Up Safety Visit	Early Termination
Study Procedure[2,3]	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**End of ETP – Continued/V≥31**	**V≥32**	**V**
Week	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**≥142**	
Day	**617**	**645**	**673**	**701**	**729**	**757**	**785**	**≥994**	
Window (day)	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±14d**	**±14d**	
PK and Immunogenicity Sampling[10]									
Blood sample for PK/Drug concentration and activin A								X	
Blood sample BMP-9								X	
Blood sample for ADA sample								X	
Biomarkers									
Blood sample for biomarker samples of bone and cartilage								X	
Blood sample for biomarker samples of inflammatory markers								X	

ADA=Antidrug antibody; BMP-9=Bone morphogenic protein 9; CAJIS= Cumulative Analog Joint Involvement Scale; CGIC=Clinician's Global Impression of Change; CT= Computed tomography; d=Day; ENT=Ear, nose, and throat; EQ-5D-3L= EuroQol 5 dimensions questionnaire with a 3-level scale; ETP=Extended Treatment Period; FOP= Fibrodysplasia ossificans progressiva; INR=International normalized ratio; PK=Pharmacokinetic; PGIC=Patient's Global Impression of Change; PGIS=Patient's Global Impression of Severity; SF-36=Short-Form 36; V=Visit; WOCBP=women of childbearing potential

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14.2.3. Footnotes for Schedule of Events for Table 4

1. After completion of the ETP (see Table 3), patients will continue extended treatment and cycle through V25 to V30 until end of study is reached (ie, last global patient completes the last study visit).
2. Procedures other than those associated with imaging procedures may be conducted by trained study staff at or near patients' residences (ie, at-home visits).
3. During the study, study procedures within each visit may be conducted on different days, within the stated visit window. If conducted on the same day, vital signs and ECG will be conducted before blood sampling, and blood samples will be collected before CT procedure.
4. All patients who receive study drug will be closely monitored after each study drug administration for at least 2 hours.
5. On study day 1 vital signs will be collected pre-dose and post-dose at 2 hours (±30 minutes) after the end of infusion. On subsequent visits, vital signs will be collected prior to dosing.
6. Menstrual history and pregnancy status of WOCBP will be determined at the screening visit. Menstrual events and pregnancy status of WOCBP will be monitored at each visit, except visit 3. A negative result for the pregnancy test must be obtained prior to each study drug administration. For both female and male patients, contraception use will be confirmed.
7. ENT consultation is to be performed during Screening Period. Follow-up visits will be conducted for patients who experience episodes of moderate or severe epistaxis, have more than three episodes of epistaxis, or if deemed necessary by the investigator.
8. In some patients, it may not be possible to obtain venous blood samples for all tests. Serum pregnancy tests and other blood tests for determining eligibility must be obtained. Blood samples for safety labs will be prioritized. Study drug administration will be performed last at that study visit.
9. A routine urinalysis will be collected in all patients (male and female). In addition, a urinalysis and urine culture will be collected in male patients experiencing an AESI related to the male reproductive system (see Section 10.1.3 in the protocol).
10. Samples for PK, ADA, total activin A, and BMP-9 analysis must be collected prior to study drug administration. In the event of a suspected SAE such hypersensitivity or anaphylaxis, additional PK and ADA samples may be collected at or near the event.

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Table 5: Schedule of Events: Observation Period

	Observation Period[1]				Follow-up Safety Visit[2]	Early Termination
Study Procedure	**V18[3]**	**V19**	**V20**	**End of Study/≥V21**	**V21**	V
Week	**60**	**68**	**76**	**≥84**	**82**	
Day	**421**	**477**	**533**	**≥589**	**574**	
Window (day)	**±7d**	**±7d**	**±7d**	**±14d**	**±7d**	
Clinical Endpoint Measures						
Phone contact	X	X	X	X	X[2]	X

d=Day; V=Visit

14.2.4. Footnotes for Schedule of Events for Table 5

1. After completion of the double-blind, placebo-controlled phase (see Table 2), patients who choose to become unblinded will enter the Observation Period and cycle through V18 to V20 until last global patient completes the last study visit.
2. Follow-Up Safety Visit is only required for patients randomized to garetosmab and scheduled 30 weeks after the last administered dose of garetosmab on week 52 (visit 16); refer to Follow-Up Safety Visit column in Table 3 for Study Procedures to be performed at this visit in these patients.
3. The first visit of the Observation Period (visit 18 [week 60]) will take place 2 months after the last dose administered (visit 16 [week 52]).

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14.2.5. Early Termination Visit

Patients who are permanently withdrawn from the study before the primary endpoint visit (week 56) will be asked to return to the clinic for an early termination visit consisting of the week 56 assessments described in Table 2.

Patients who are permanently withdrawn from the study before the end of the ETP or the Observation Period will be asked to return to the clinic for an early termination visit consisting of the assessments described in Table 3, Table 4, and Table 5.

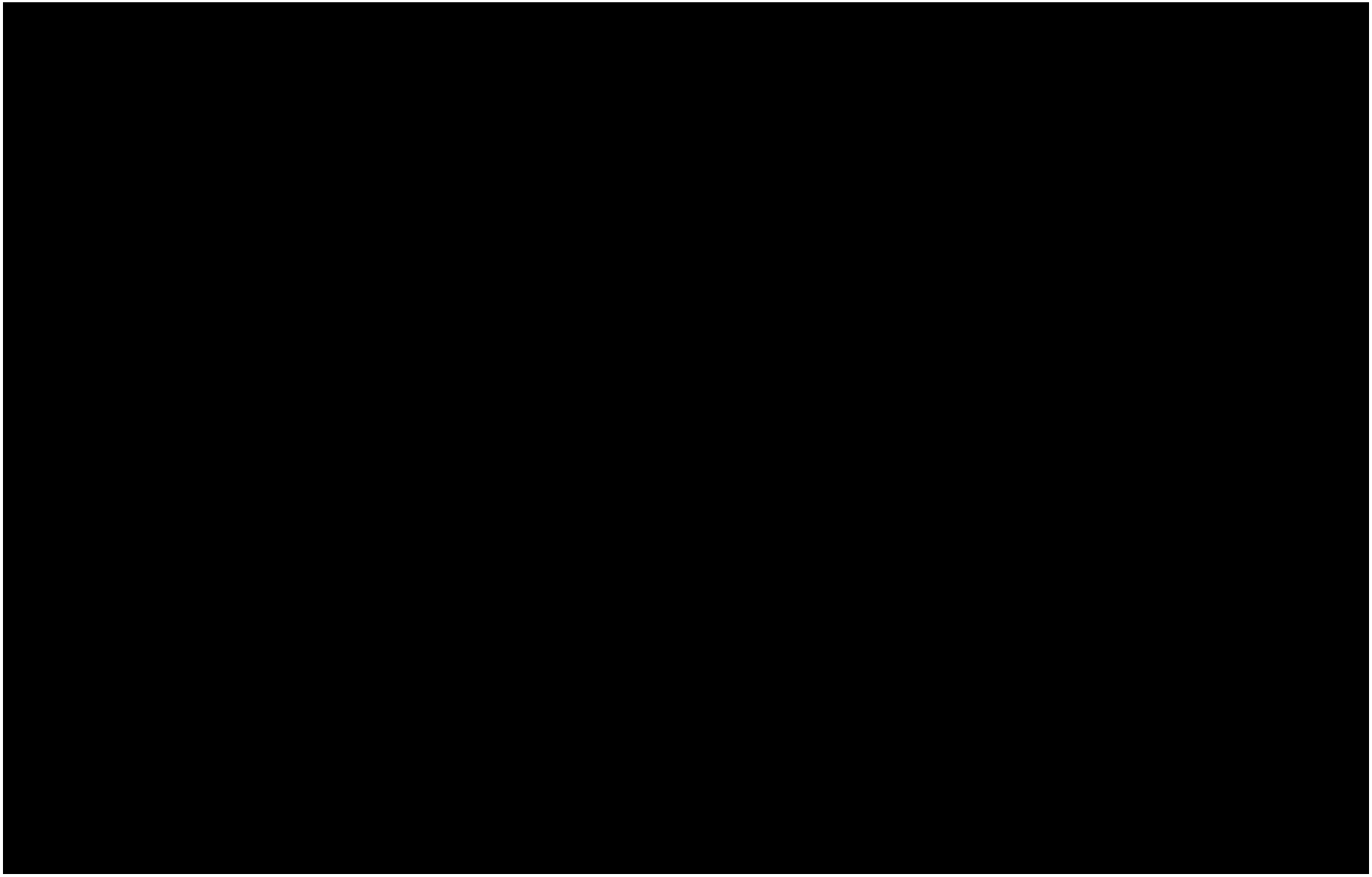
Note, patients who permanently discontinue from study drug and agree to continue follow-up do not need to be terminated from the study (see Section 8.2.2 in the protocol).

14.2.6. Unscheduled Visits

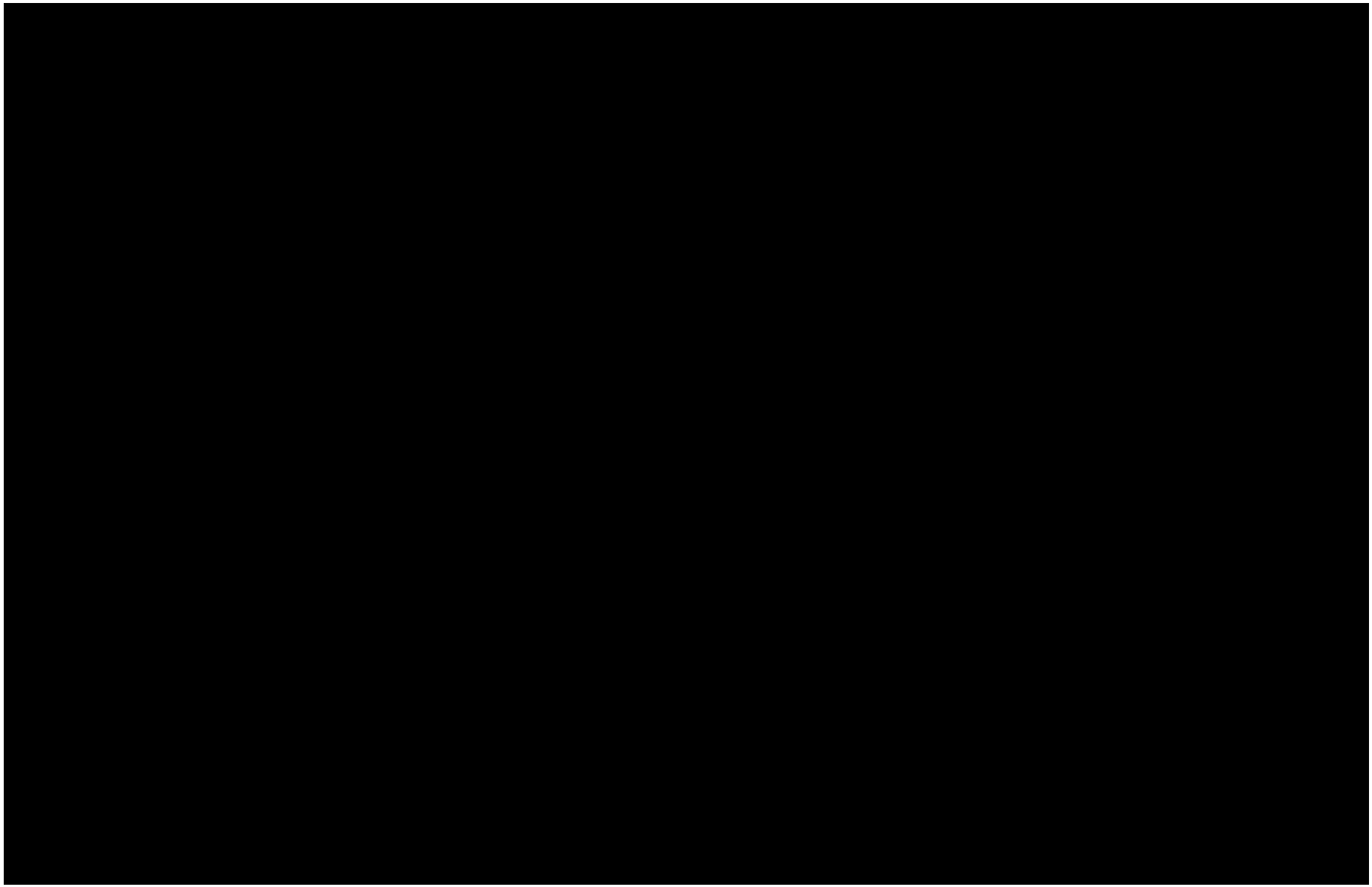
All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs (eg, if bleeding event occurs [see Section 3.3.2 in the protocol]), or for any other reason, as warranted.

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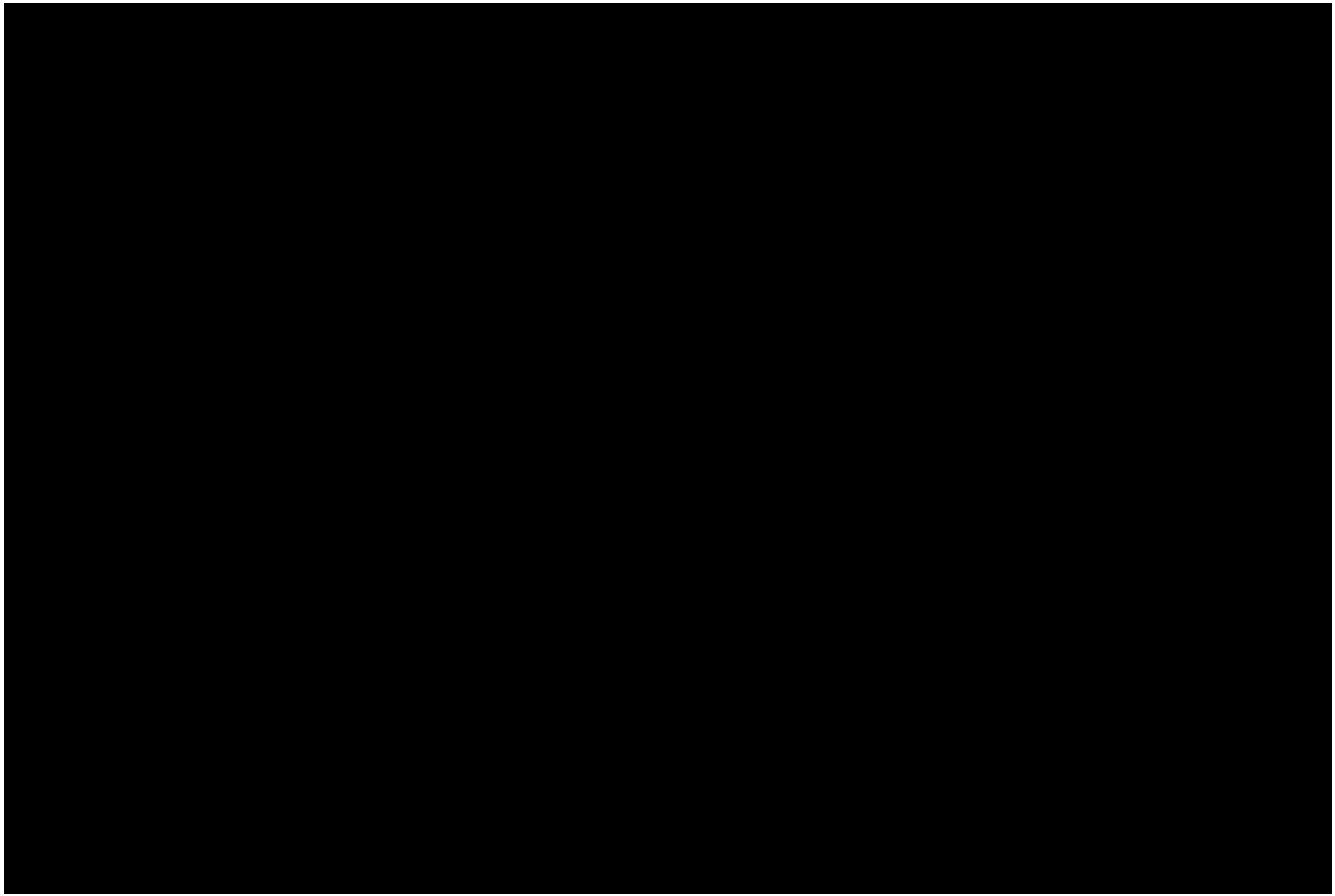
14.3. Criteria for Potentially Clinically Significant Values (PCSV)



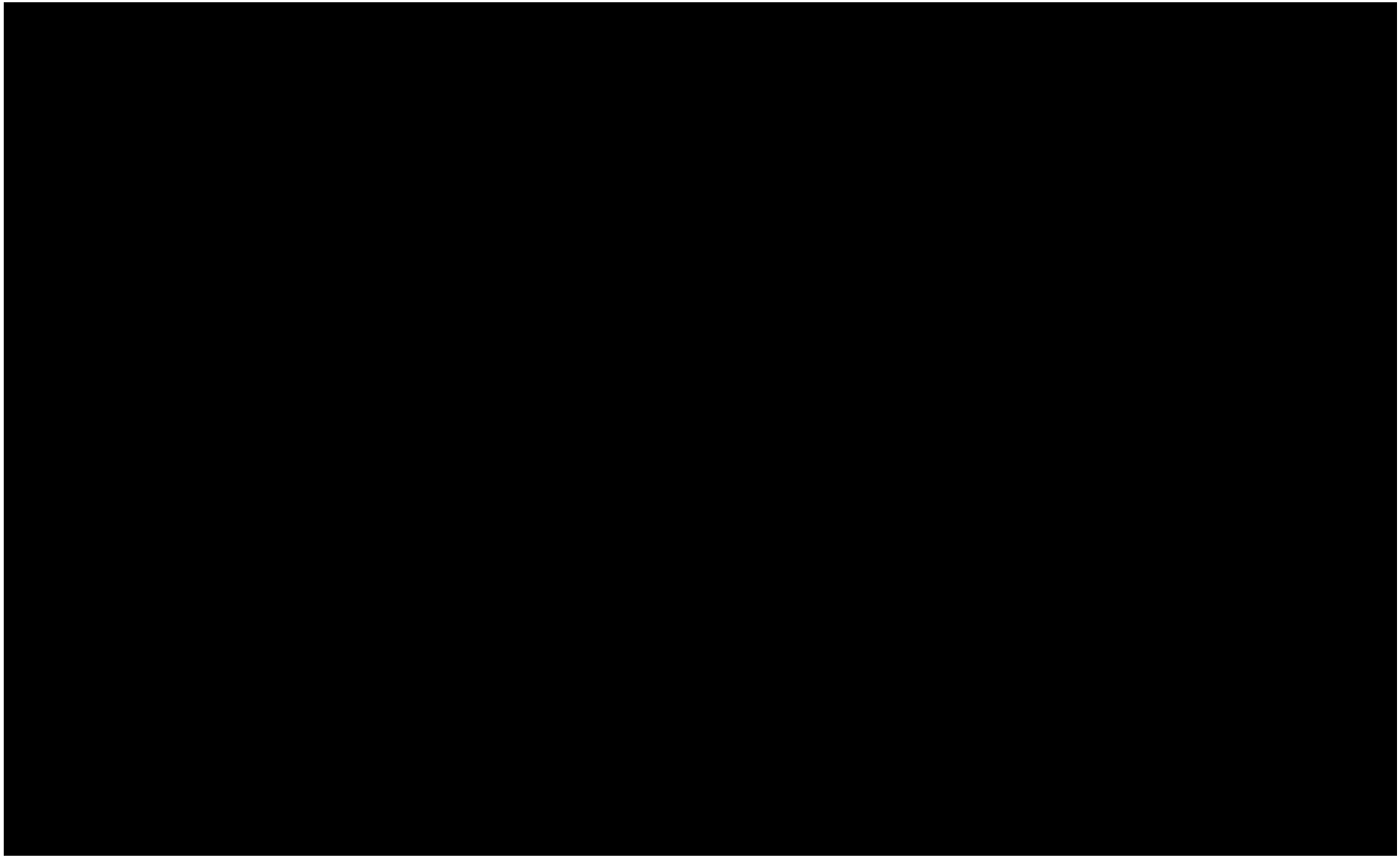
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14.4. Analysis Visit Windows

Time Window for Efficacy Variables:

Visit No.	Visit	Targeted Study Day	Measurements from CT	CAJIS, EQ-5D-3L, SF-36, PGIS	PGIC, CGIC	Spirometry (FVC/FEV-1)	Clinician-assessed Flare	Patient-reported Flare
1	Screening	<1	<1	<1		<1		
2	Baseline	1					1	1
3	Week 1	8					[2, 18]	[2, 18]
4	Week 4	29					[19, 42]	[19, 42]
5	Week 8	57					[43, 70]	[43, 70]
6	Week 12	85					[71, 98]	[71, 98]
7	Week 16	113					[99, 126]	[99, 126]
8	Week 20	141					[127, 154]	[127, 154]
9	Week 24	169					[155, 182]	[155, 182]
10	Week 28	197	[1, 294]	[1, 294]	[1, 294]	[1, 294]	[183, 212]	[183, 212]
11	Week 32	225					[213, 238]	[213, 238]
12	Week 36	253					[239, 266]	[239, 266]
13	Week 40	281					[267, 294]	[267, 294]
14	Week 44	309					[295, 322]	[295, 322]
15	Week 48	337					[323, 350]	[323, 350]
16	Week 52	365					[351, 378]	[351, 378]
17	Week 56	393	[295, 490]	[295, 490]	[295, 490]	[295, 490]	[379, 406]	≥379
18	Week 60	421					[407, 434]	
19	Week 64	449					[435, 462]	
20	Week 68	477					[463, 490]	
21	Week 72	505					[491, 518]	
22	Week 76	533					[519, 546]	
23	Week 80	561					[547, 574]	
24	Week 84	589	≥491	[491, 672]	[491, 672]		[575, 602]	
25	Week 88	617					[603, 630]	

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26	Week 92	645					[631, 658]	
27	Week 96	673					[659, 686]	
28	Week 100	701					[687, 714]	
29	Week 104	729					[715, 742]	
30	Week 108	757		[673, 770]	[673, 770]		[743, 770]	
31	Week 112	785		≥771	≥771		≥771	

Time Window for Safety Variables:

Visit No.	Visit	Targeted Study Day	Lab (Hematology, Blood chemistry, Urinalysis)	Lab (Platelet flow cytometry)	Lab (Coagulation parameters)	Vital Sign	ECG
1	Screening	<1	<1	<1	<1	<1	<1
2	Baseline	1	1	1	1	1	
3	Week 1	8				[2, 18]	
4	Week 4	29	[2, 42]	[2, 42]		[19, 42]	
5	Week 8	57	[43, 70]	[43, 70]		[43, 70]	
6	Week 12	85	[71, 98]	[71, 98]	[2, 140]	[71, 98]	
7	Week 16	113	[99, 126]	[99, 126]		[99, 126]	
8	Week 20	141	[127, 168]			[127, 154]	
9	Week 24	169				[155, 182]	
10	Week 28	197	[169, 238]	[127, 238]	[141, 238]	[183, 212]	[1, 294]
11	Week 32	225				[213, 238]	
12	Week 36	253				[239, 266]	
13	Week 40	281	[239, 336]	[239, 336]	[239, 336]	[267, 294]	
14	Week 44	309				[295, 322]	
15	Week 48	337				[323, 350]	
16	Week 52	365				[351, 378]	
17	Week 56	393	[337, 434]	[337, 434]	[337, 434]	[379, 406]	[295, 490]
18	Week 60	421				[407, 434]	
19	Week 64	449				[435, 462]	
20	Week 68	477	[435, 532]		[435, 532]	[463, 490]	

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21	Week 72	505				[491, 518]	
22	Week 76	533				[519, 546]	
23	Week 80	561				[547, 574]	
24	Week 84	589	[533, 672]	≥435	[533, 672]	[575, 602]	[491, 686]
25	Week 88	617				[603, 630]	
26	Week 92	645				[631, 658]	
27	Week 96	673				[659, 686]	
28	Week 100	701				[687, 714]	
29	Week 104	729				[715, 742]	
30	Week 108	757	[673, 770]		[673, 770]	[743, 770]	
31	Week 112	785	≥771		≥771	≥771	≥687

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