Statistical Analysis Plan

Protocol Title:	A Phase 3, Randomized, 52-week, Placebo-controlled, Double-blind Study With Re-randomization to Assess the Efficacy, Safety, and Tolerability of Rocatinlimab (AMG 451) in Adolescent Subjects With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-ASTRO)
Short Protocol Title:	Phase 3, 52-week Study Evaluating Rocatinlimab (AMG 451) in Adolescent Subjects With Moderate-to-severe AD (ROCKET-ASTRO)
Protocol Number:	20210145
NCT Number:	NCT05704738
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SAP Date:	**Document Version** — **Date** **Original (v1.0)** — 19 June 2025 **Amendment 1 (v2.0)** — 11 September 2025

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	19JUN2025	Original
Amendment 1 (v2.0)	11SEP2025	• Section 5.1.1: clarified that the erroneous SCORAD score for 35 visits from 8 subjects will be excluded from the analysis. • Section 6.2: clarified that safety data will be summarized by randomized and rerandomized/assigned treatment for post week 24.

		• Section 6.3: defined the safety analysis set for the entire study and clarified that the safety data will be summarized by assigned treatment for the entire study. • Section 9.5.1.2 and Table 9-2: To maintain consistency across studies within the program and address [redacted] the hypothetical strategy for handling both intercurrent events of 4 and 5 in the maintenance primary estimand was changed to the treatment policy strategy, where observed data during the maintenance treatment period after the 2 intercurrent events will be kept in the analysis. • Section 9.5.2.2: clarified that the LOCF during maintenance treatment period includes data starting at week 24. • [redacted] • Section 9.6: clarified that assigned treatments will be used to summarize pooled safety data during the entire study • Section 10: added the deviation from the protocol regarding replacing hypothetical strategy with treatment policy strategy for 2 of the intercurrent events in maintenance primary estimand

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List of Abbreviations

Abbreviation	Explanation
AD	atopic dermatitis
ALP	alkaline phosphatase
ALT	alanine aminotransaminase
ANCOVA	analysis of covariance
AST	aspartate aminotransaminase
BOCF	Baseline observation carried forward
[redacted]	[redacted]
CDLQI	Children's Dermatology Life Quality Index
[redacted]	
COVID-19	coronavirus disease-19
CRF	case report form
CSR	clinical study report
C_{trough}	concentration trough
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
[redacted]	
EASI 75	achievement of ≥ 75% reduction from baseline in EASI score
EASI 90	achievement of ≥ 90% reduction from baseline in EASI score
[redacted]	
eCOA	electronic Clinical Outcome Assessments
[redacted]	
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EOI	event of interest
EOS	end of study
EOT	end of treatment
[redacted]	
FAS	full analysis set
[redacted]	
[redacted]	
GBS	Global Biostatistical Science
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale

[redacted]	
IGA	Investigator's Global Assessment
IPD	Important protocol deviation
JAK	janus kinase
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
[redacted]	
MT	maintenance treatment
[redacted]	
NRS	numeric rating scale
NICE	National Institute of Health and Care Excellence
OLT	open-label treatment
OLRT	open-label retreatment
[redacted]	
[redacted]	
POEM	Patient Oriented Eczema Measure
PRO	patient-reported outcome
Q4W	every 4 weeks
QTc	corrected QT interval
Q8W	every 8 weeks
REGPMM	regression and predictive mean matching
rIGA™	revised Investigator's Global Assessment
rIGA 0/1	achieving vIGA-AD 1 response with presence of only barely perceptible erythema or vIGA-AD 0 response and ≥ 2-point reduction from baseline
SAP	statistical analysis plan
SCORAD	SCORing atopic dermatitis
SFU	safety follow-up
TBL	total bilirubin
[redacted]	
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
US	United States
VAS	Visual Analog Scale

vIGA-AD™	Validated Investigator's Global Assessment for Atopic Dermatitis
vIGA-AD 0/1	Achieving a vIGA-AD score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline
vIGA-AD 0	Achieving a vIGA-AD score of 0 (clear) with ≥ 2-point reduction from baseline
vIGA-AD 1	Achieving a vIGA-AD score of 1 (almost clear) with ≥ 2-point reduction from baseline
WOCF	Worst observation carried forward
[redacted]	

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 6 for study 20210145, Rocatinlimab (AMG 451) dated March 28 2025. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science (GBS) department unless otherwise specified.

2. Objectives, Endpoints/Estimands and Hypotheses

2.1 Objectives and Endpoints/Estimands

[redacted]

Objectives	Endpoints
Primary	
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24, assessed using validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™)	• Achieving a vIGA-AD score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline (vIGA-AD 0/1) at week 24
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24, assessed using Eczema Area and Severity Index (EASI)	• Achieving ≥ 75% reduction in EASI score from baseline (EASI 75) at week 24
Key Secondary	
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 16, assessed using EASI	• Achieving EASI 75 at week 16

• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 16, assessed using vIGA-AD	• Achieving vIGA-AD 0/1 at week 16
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 16 and at week 24 on the patient-reported outcome (PRO) measure of pruritus	• Achieving ≥ 4-point reduction from baseline in weekly average of daily worst pruritus numeric rating scale (NRS) score at week 16 in subjects with baseline weekly average of daily worst pruritus NRS score ≥ 4 • Achieving ≥ 4-point reduction from baseline in weekly average of daily worst pruritus NRS score at week 24 in subjects with baseline weekly average of daily worst pruritus NRS score ≥ 4
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24, assessed using EASI	• Achieving ≥ 90% reduction in EASI score from baseline (EASI 90) at week 24
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24 on the PRO measure of atopic dermatitis (AD) skin pain	• Achieving ≥ 4-point reduction from baseline in weekly average of AD skin pain NRS score at week 24 in subjects with baseline weekly average of AD skin pain NRS score ≥ 4
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24, assessed using vIGA-AD with an additional assessment of morphology	• Achieving vIGA-AD 1 with presence of only barely perceptible erythema or vIGA-AD 0 (revised Investigator's Global Assessment [rIGA™] 0/1) at week 24
Other Secondary	
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo on use of rescue medication at week 16 and week 24	• Initiation of rescue medication for AD at or before week 16 • Initiation of rescue medication for AD at or before week 24
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 16 and week 24 on the PRO measure of pruritus	• Change from baseline in weekly average of daily worst pruritus NRS score at week 16 • Change from baseline in weekly average of daily worst pruritus NRS score at week 24 • Change from baseline in SCORing atopic dermatitis (SCORAD) itch Visual Analog Scale (VAS) score at week 16

	• Change from baseline in SCORAD itch VAS score at week 24
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24, assessed by the Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI)	For subjects ≥ 16 years old at enrollment • Achieving ≥ 4-point reduction from baseline in DLQI score at week 24 in subjects with baseline DLQI score ≥ 4 • Change from baseline in DLQI score at week 24 For subjects < 16 years old at enrollment • Change from baseline in CDLQI score at week 24
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24 on the PRO measure of Patient Oriented Eczema Measure (POEM)	• Achieving ≥ 4-point reduction from baseline in POEM score at week 24 in subjects with baseline POEM score ≥ 4 • Change from baseline in POEM score at week 24
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 16 and week 24 on the PRO measure of AD skin pain	• Achieving ≥ 4-point reduction from baseline in weekly average of AD skin pain NRS score at week 16 in subjects with baseline weekly average of AD skin pain NRS score ≥ 4 • Change from baseline in weekly average of daily AD skin pain NRS score at week 24 • Change from baseline in weekly average of daily AD skin pain NRS score at week 16 • Achieving ≥ 3-point reduction from baseline in weekly average of AD skin pain NRS score at week 24 in subjects with baseline weekly average of AD skin pain NRS score ≥ 3 • Achieving ≥ 3-point reduction from baseline in weekly average of AD skin pain NRS score at week 16 in subjects with baseline weekly average of AD skin pain NRS score ≥ 3
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24 on the PRO measure of sleep disturbance	• Change from baseline in weekly average of sleep disturbance NRS score at week 24
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg	• Achieving HADS-anxiety subscale score < 8 at week 24 in subjects with

compared with placebo at week 24 on the PRO measure of anxiety using the Hospital Anxiety and Depression Scale (HADS)	baseline HADS-anxiety subscale score ≥ 8 • Achieving HADS-depression subscale score < 8 at week 24 in subjects with baseline HADS-depression subscale score ≥ 8 • Change from baseline in HADS-anxiety subscale score at week 24 • Change from baseline in HADS-depression subscale score at week 24
• To evaluate the efficacy of rocatinlimab 300 mg and 150 mg compared with placebo at week 24 using the SCORAD	• Achieving ≥ 8.7-point reduction from baseline in SCORAD score at week 24 in subjects with baseline SCORAD score ≥ 8.7
Safety and Immunogenicity	
• To characterize the safety and tolerability of rocatinlimab	• Treatment-emergent adverse events (including clinically significant changes in laboratory values and vital signs) and serious adverse events
[redacted]	

Estimand(s) for Primary Objective(s)

Two intercurrent events will be considered to estimate the treatment effects: initiation of rescue therapy for AD (Appendix B) and permanent discontinuation of investigational product without rescue therapy for AD. Subjects are encouraged to continue all remaining study visits and procedures**,** with the exception of investigational product administration and post-dose monitoring procedures, through week 24 or week 52 after permanent discontinuation of investigational product for evaluation of endpoints.

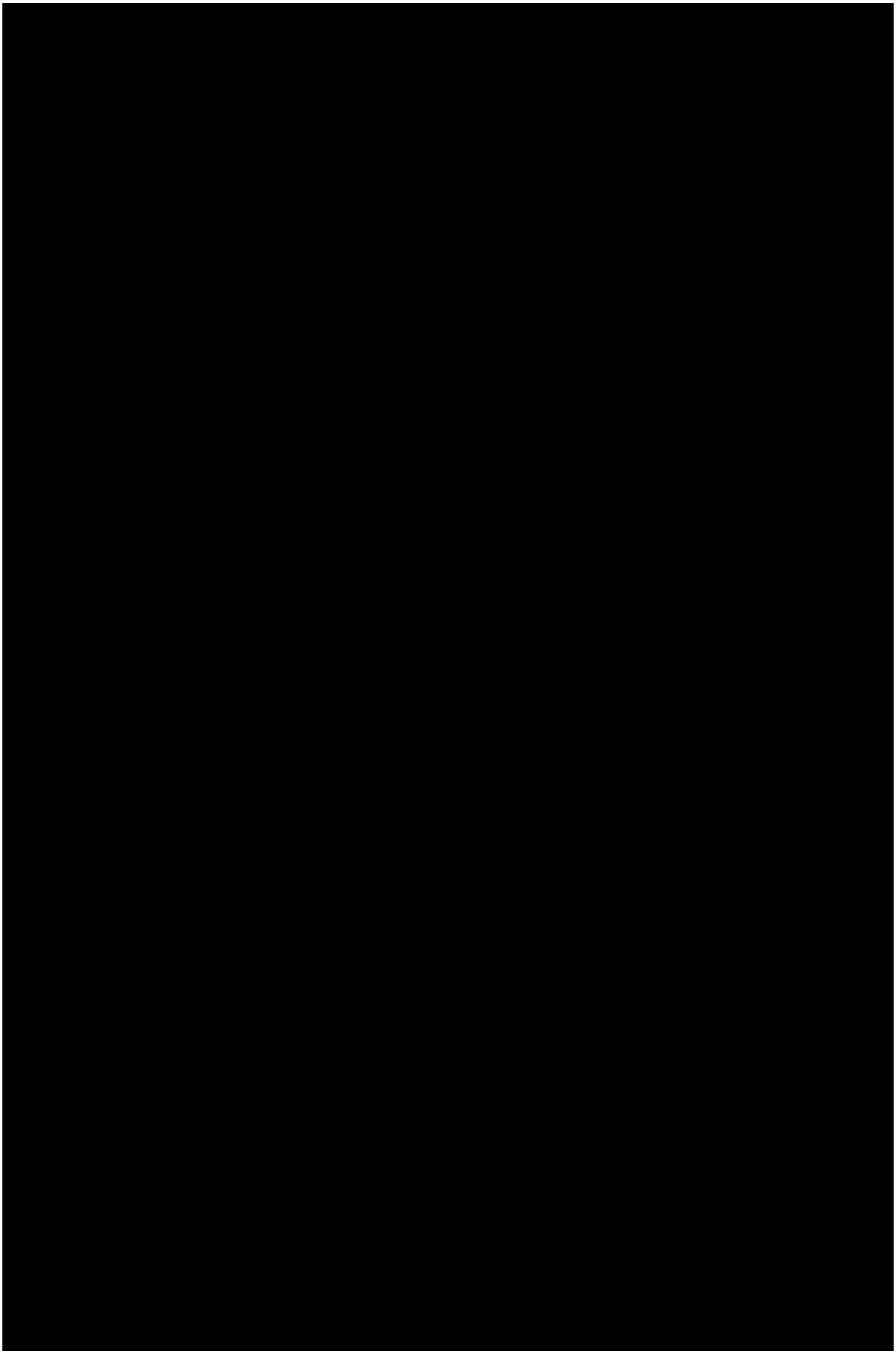
The primary estimand for a binary endpoint is to measure the effect of rocatinlimab as assessed by the difference in response rates between each of the 2 rocatinlimab treatment groups (300 mg and 150 mg) and placebo, combining both monotherapy and combination therapy cohorts, among randomized subjects within moderate-to-severe AD population without rescue therapy for AD, regardless of permanent discontinuation of investigational product. Subjects initiating rescue therapy for AD will be classified as nonresponders at all subsequent time points (composite strategy reflecting lack of response). For subjects who do not use rescue therapy for AD but permanently

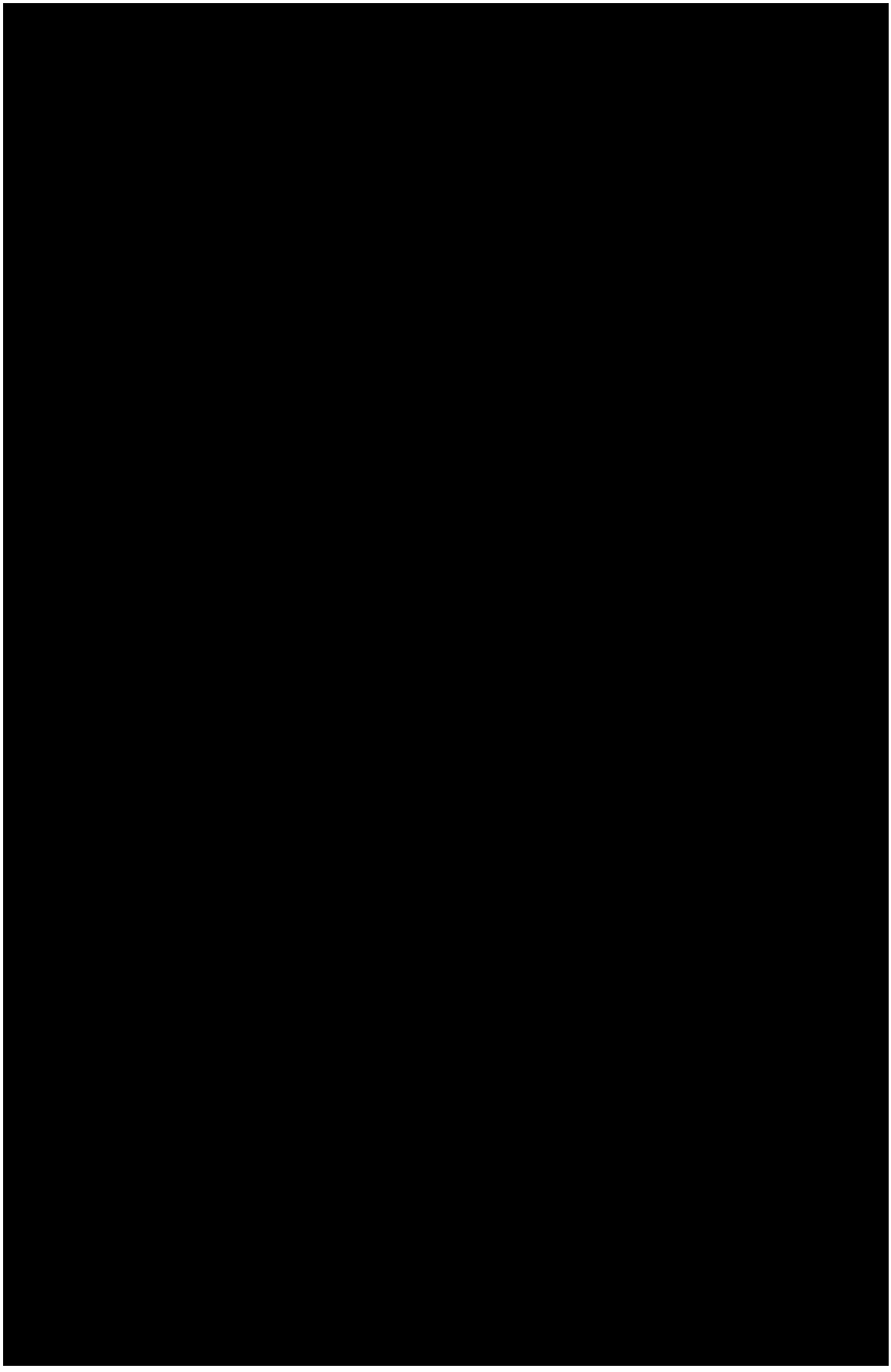
discontinue investigational product, data retrieved after study treatment discontinuation will be included as collected (treatment policy strategy).

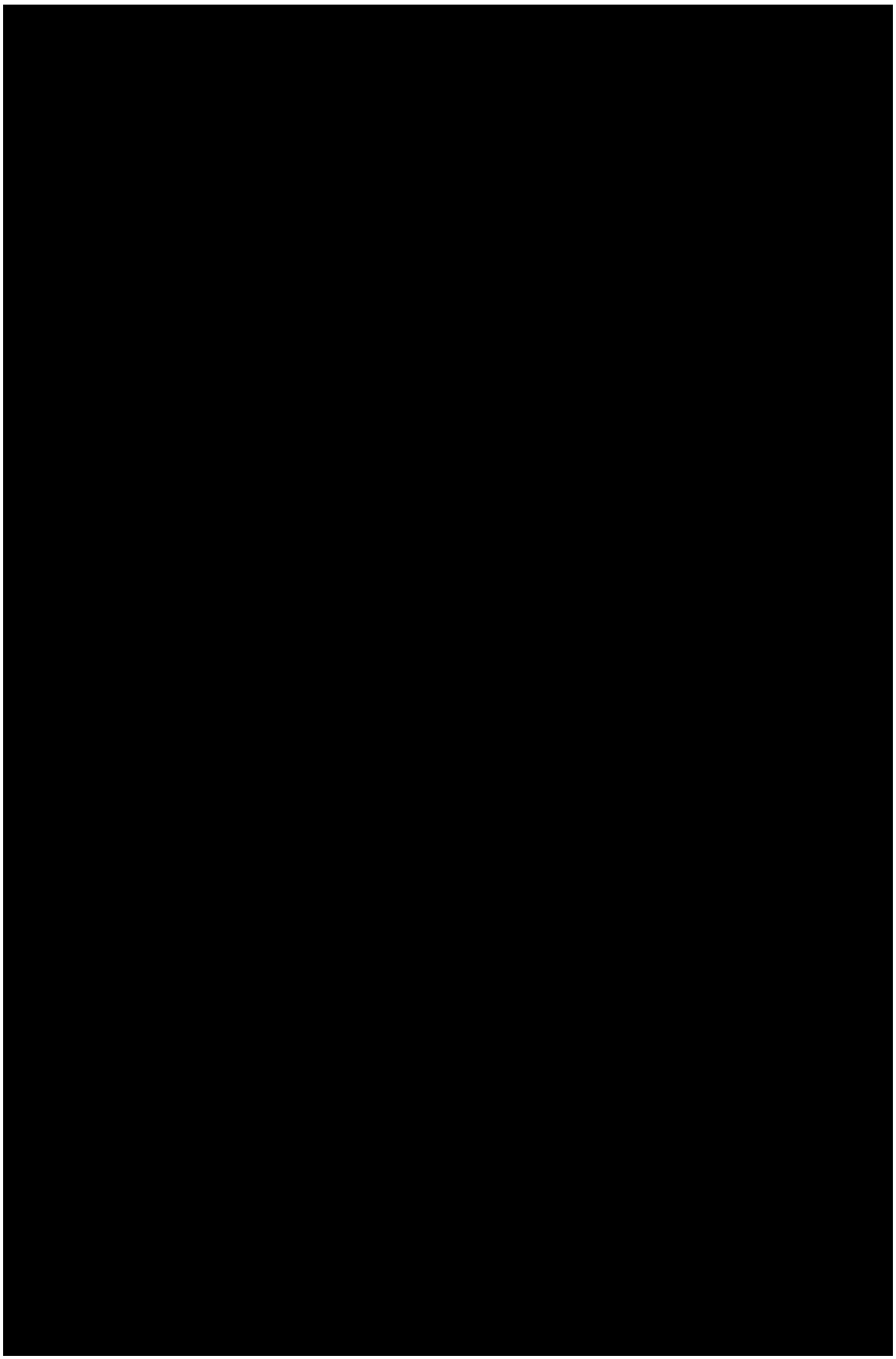
The primary estimand for a continuous endpoint is to measure the effect of rocatinlimab as assessed by the difference in means of change or percent change from baseline value between each of the 2 rocatinlimab treatment groups (300 mg and 150 mg) and placebo, combining both monotherapy and combination therapy cohorts, among randomized subjects within moderate-to-severe AD population without rescue therapy for AD, regardless of permanent discontinuation of investigational product. Subjects initiating rescue therapy for AD will be included in the analysis, and each subject's worst observation, including baseline value, before initiation of rescue therapy for AD will be carried forward (worst observation carried forward [WOCF]) to all subsequent time points (composite strategy reflecting lack of response). For subjects who do not use rescue therapy for AD but permanently discontinue investigational product, data retrieved after permanent discontinuation of investigational product will be included as collected (treatment policy strategy).

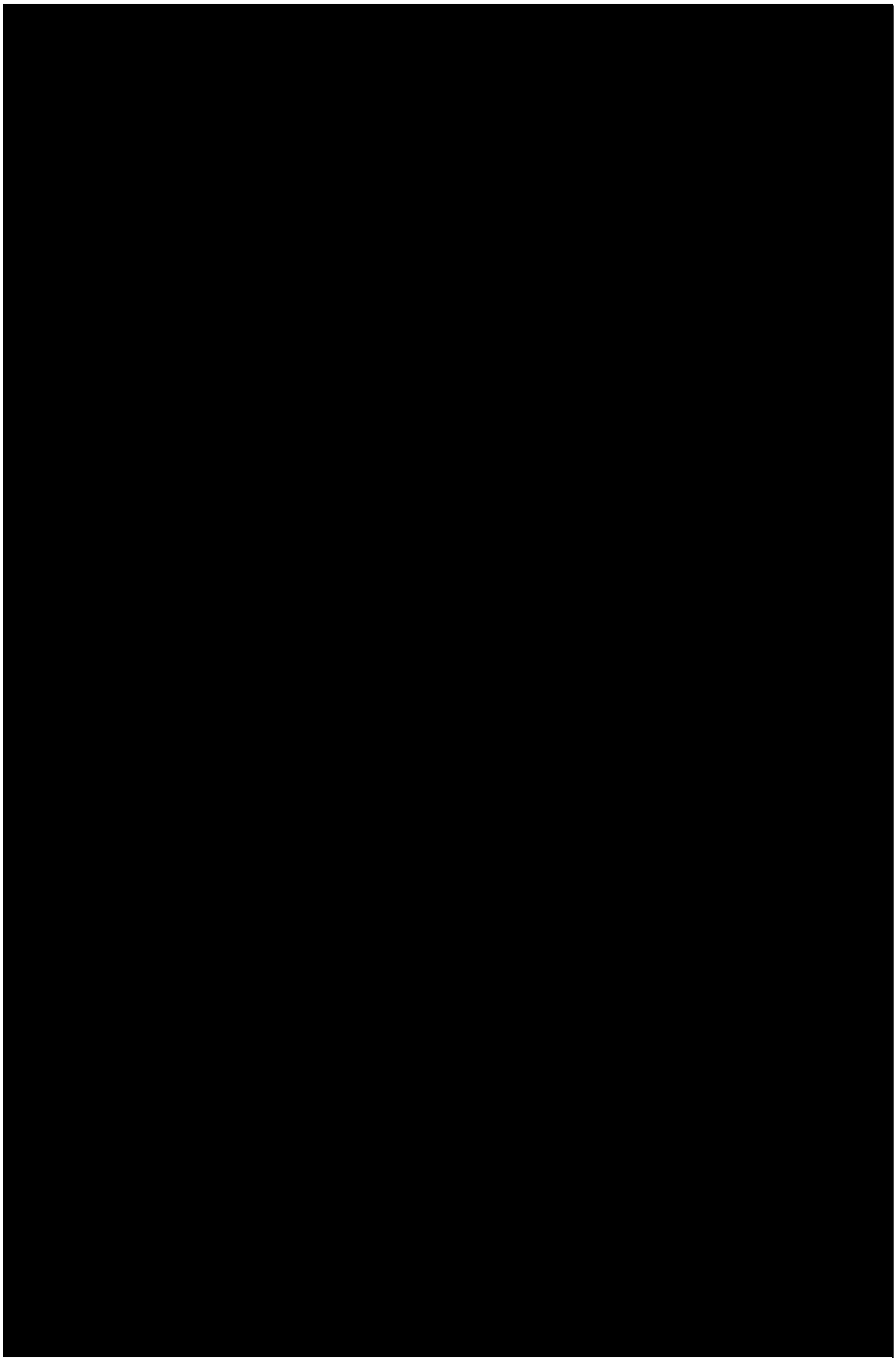
Additional supportive estimands are defined in Section 9.5.1.

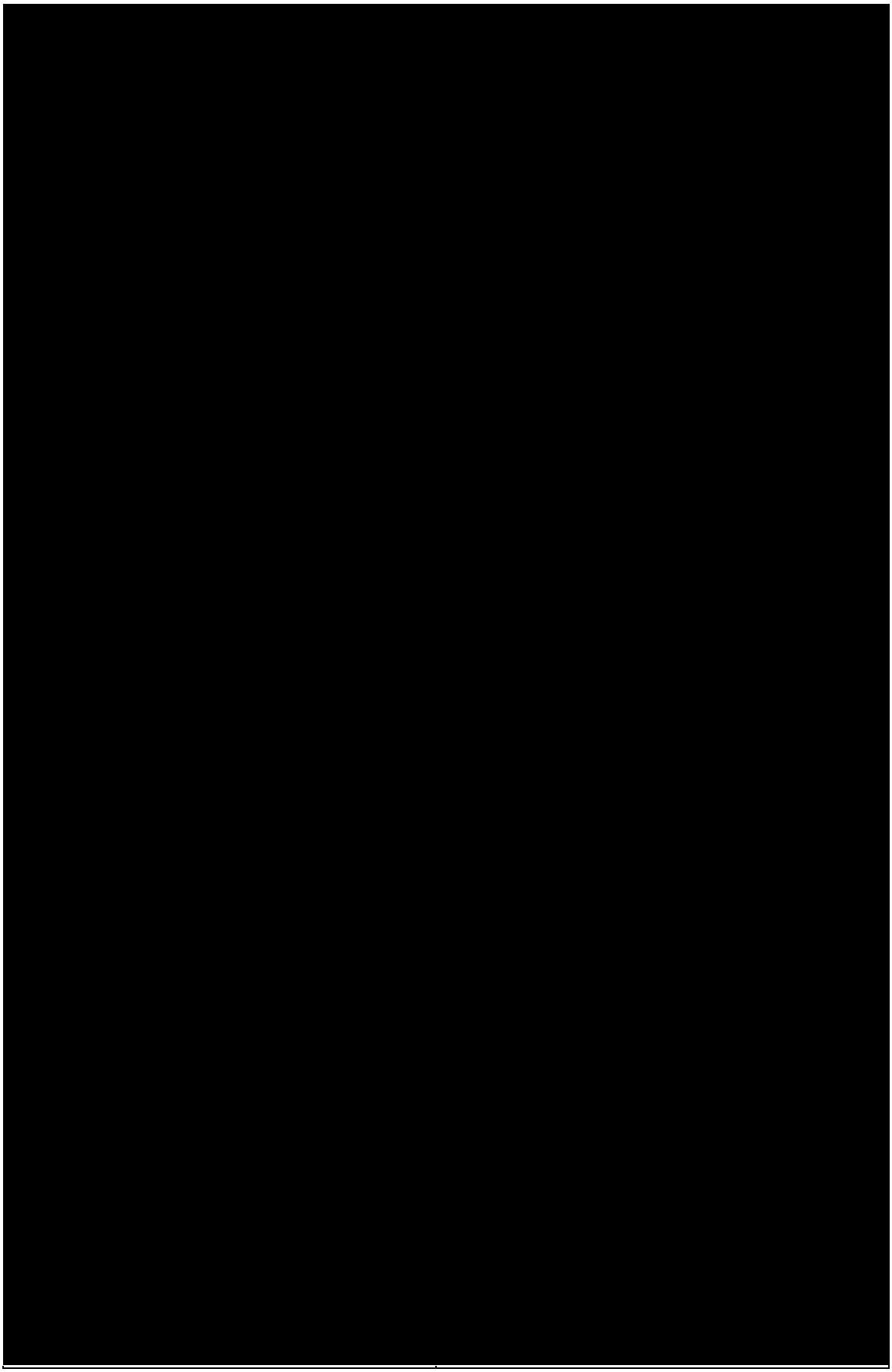
Exploratory (First 24-Week Treatment Period)
[redacted]

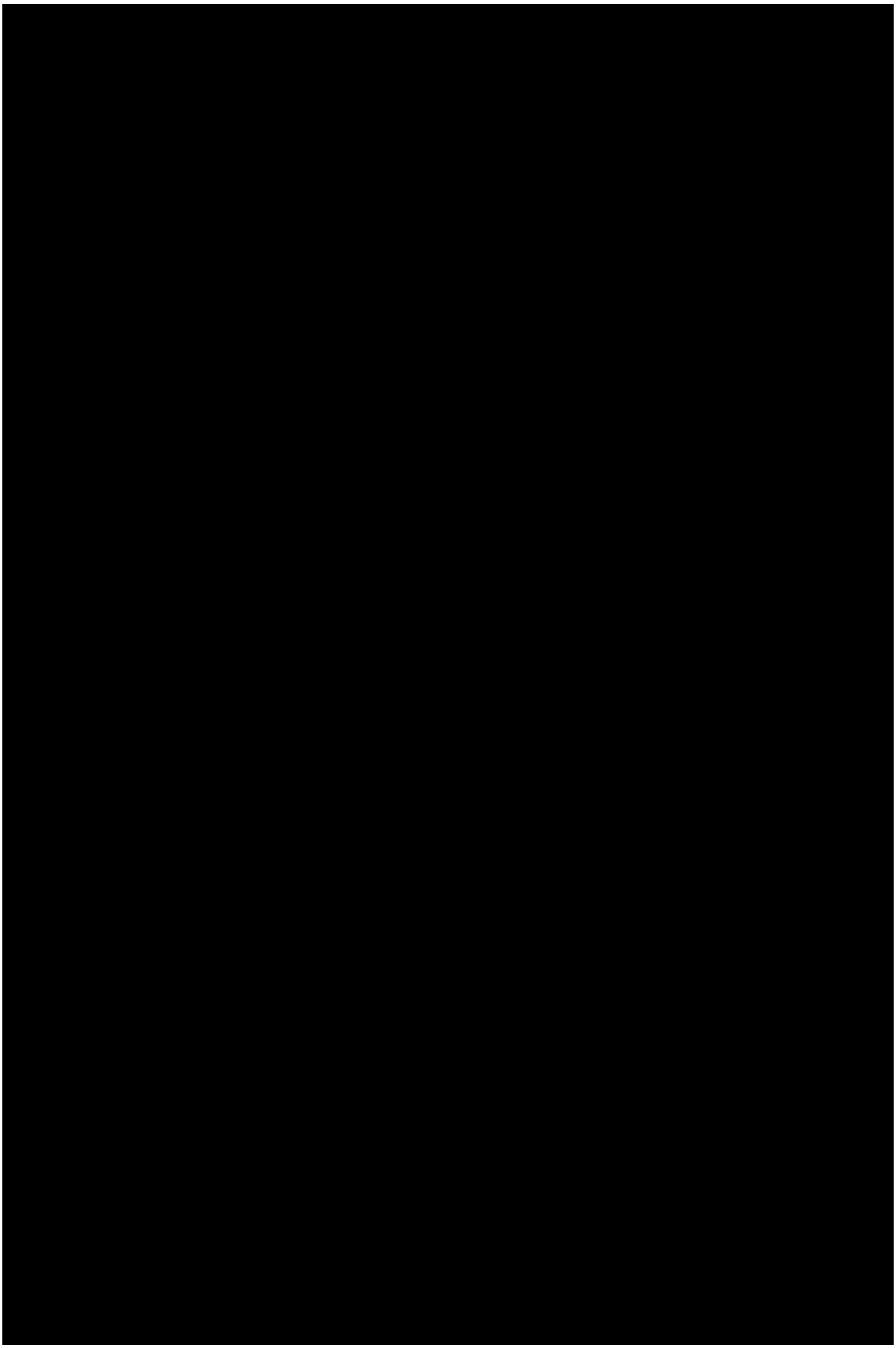


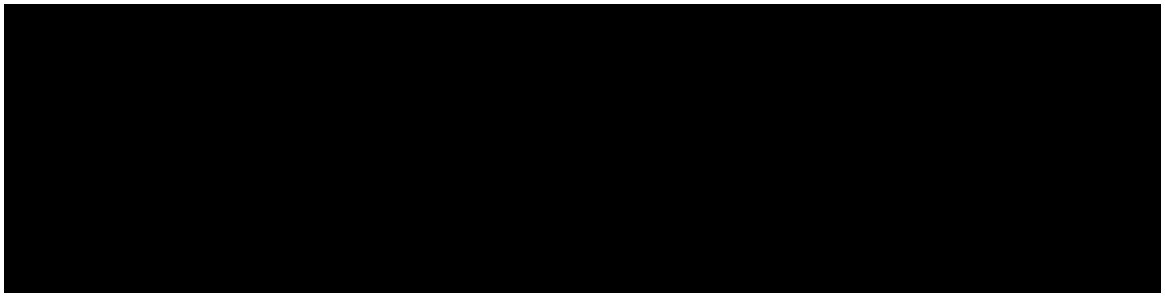












2.2 Hypotheses and/or Estimations

The primary hypothesis is that either rocatinlimab 300 mg or 150 mg is superior to placebo as treatment in subjects with moderate-to-severe AD, as assessed by the co-primary endpoints (vIGA-AD 0/1 response at week 24 and an EASI 75 response at week 24).

Both coprimary endpoints need to achieve statistical significance to declare success for each rocatinlimab dose.

3. Study Overview

3.1 Study Design

This is a phase 3, 52-week, randomized, double-blind, placebo-controlled study with rerandomization to evaluate the efficacy, safety, and tolerability of rocatinlimab monotherapy or in combination with TCS and/or TCI in approximately 500 adolescent subjects with moderate-to-severe AD with inadequate response to topical medications.

Initiation Treatment Period

Approximately [redacted] eligible subjects will be randomized in a [redacted] ratio to 3 treatment groups within the monotherapy or combination therapy cohort for a duration of 24 weeks as follows:

- Rocatinlimab 300 mg every 4 weeks (Q4W) (with a loading dose at week 2) (+ TCS/TCI for combination therapy cohort) (N = [redacted])
- Rocatinlimab 150 mg Q4W (with a loading dose at week 2) (+ TCS/TCI for combination therapy cohort) (N = [redacted])
- Placebo Q4W (with a loading dose at week 2) (+ TCS/TCI for combination therapy cohort) (N = [redacted])

Randomization will be stratified by cohort (monotherapy cohort vs combination therapy cohort at the investigator's discretion, in discussion with the subject and their parent/guardian and consideration of the combination therapy study inclusion criteria), baseline disease severity (vIGA-AD score of 3 [moderate] vs 4 [severe]) and geographic region (Japan vs non-Japan Asian countries vs rest of world).

Maintenance Treatment (MT) Period for Responders

- At the week 24 visit, subjects who are initially randomized to either rocatinlimab treatment group and achieve [redacted] will be re-randomized within monotherapy or combination therapy cohort to the 28-week maintenance treatment as follows:

- Subjects in the initially randomized rocatinlimab 300 mg Q4W group will be rerandomized [redacted] into:
  - Rocatinlimab 300 mg Q4W (+ TCS/TCI for combination therapy cohort)
  - Rocatinlimab 300 mg every 8 weeks (Q8W) (+ TCS/TCI for combination therapy cohort)
- Subjects in the initially randomized rocatinlimab 150 mg Q4W group will be rerandomized [redacted] into:
  - Rocatinlimab 150 mg Q4W (+ TCS/TCI for combination therapy cohort)
  - Rocatinlimab 150 mg Q8W (+ TCS/TCI for combination therapy cohort)

Re-randomization will be stratified by cohort (monotherapy cohort vs combination therapy cohort), geographic region (Japan vs non-Japan Asia countries vs rest of world), and vIGA-AD score at week 24 (0 vs 1 vs ≥ 2).

Subjects who are initially randomized to placebo and achieve [redacted]

Subjects randomized to Q8W regimens will receive placebo during the weeks when rocatinlimab is not administered.

Open-label Treatment (OLT) Period for Nonresponders

[redacted]

A protocol-defined stopping rule will apply to subjects who do not demonstrate an adequate benefit after [redacted] weeks of open-label treatment ([redacted]).

Subjects may continue open-label treatment if any of the following criteria are met:

[redacted]

[redacted]

Subjects who do not meet any of these criteria after [redacted] weeks of open-label treatment will discontinue open-label investigational product at that visit (ie, end of treatment [EOT] visit) and complete the safety follow-up visit [redacted] weeks after the last dose of open-label investigational product.

Open-label Retreatment (OLRT) Upon Relapse

During the 28-week blinded maintenance treatment period, subjects who meet the criteria of relapse [redacted]

[redacted]

[redacted]]) will be assigned to receive open-label rocatinlimab 300 mg Q4W for the remainder of the study.

A protocol defined stopping rule will apply to subjects who do not demonstrate an adequate benefit after [redacted] weeks of open-label retreatment.

Subjects may continue open-label retreatment if any of the following criteria are met:

[redacted]

Subjects who do not meet any of these criteria after [redacted] weeks of open-label retreatment will discontinue investigational product at that visit (ie, EOT visit) and complete the safety follow-up visit [redacted] weeks after the last dose of open-label investigational product.

Rescue Therapies for AD

For the monotherapy cohort, use of [redacted]

[redacted] during the 52-week study will be considered use of rescue therapy in the analysis.

For the combination therapy cohort, starting on day 1, subjects will use concomitant low-to-medium [redacted], which could be tapered or stopped and

restarted, as clinically required, at the discretion of investigator, during the study. Use of [redacted] during the 52-week study will be considered use of rescue therapy in the analysis.

Allowed rescue therapies are those approved for treatment of AD as well as local standard of care. Subjects may continue investigational product if there is concurrent use of topical rescue therapies (excluding topical JAK inhibitors) or phototherapy. Subjects must permanently discontinue investigational product if there is use of prohibited therapies, systemic corticosteroids, conventional non-biologic, non-targeted immunosuppressive systemic therapies, biologics, targeted systemic AD rescue therapies, or topical JAK inhibitors.

Discontinuation of Study Treatment and Subject Discontinuation

Subjects who permanently discontinue investigational product for any reason before or after week 24 are encouraged to complete all remaining study visits and procedures, with the exception of investigational product administration and post-dose monitoring procedures, through week 24 or week 52, respectively, for evaluation of endpoints. Subjects who permanently discontinue investigational product and do not complete the remaining study visits through week 52 should complete an EOT visit at the next scheduled visit following the last dose of the investigational product.

Safety Follow-up

A safety follow-up (SFU) visit is required [redacted] weeks after the last dose of investigational product for all subjects who do not enroll into the maintenance study (Study [redacted].

The maximum study duration for a single subject will be approximately [redacted]

[redacted]

3.2 Sample Size

[redacted]

[redacted] rocatinlimab 150 mg and placebo for achieving vIGA-AD 0/1 at week 24 with a [redacted]. Furthermore, the same sample size will [redacted]. The assumed response rate is based on the current [redacted]. In addition, the proposed sample size will ensure [redacted] With respect to the safety evaluation, the proposed sample size of [redacted] and [redacted] for the rocatinlimab 300 mg and 150 mg treatment groups will provide [redacted]

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

All analyses of efficacy endpoints during initiation treatment period will be adjusted for the effect of the stratification factors, including cohort (monotherapy cohort vs combination therapy cohort), baseline disease severity (vIGA-AD score of 3 [moderate] versus 4 [severe]), and geographic region (Japan versus non-Japan Asian countries versus rest of world), as well as baseline value of the efficacy endpoint of interest, when applicable. Levels in stratification factors with few subjects will be combined with the closest level.

4.2 Subgroups

The following coprimary and selected key secondary endpoints

- Achieving vIGA 0/1 at week 24 (coprimary endpoint for ex-US and key secondary endpoint for US)
- Achieving rIGA 0/1 at week 24 (coprimary endpoint for US)
- Achieving EASI 75 at week 24 (coprimary endpoint for ex-US and US)

will be analyzed by but not limited to the subgroups listed below:

- Cohort (monotherapy, combination therapy)
- Sex (male, female)
- Geographic region (Japan, non-Japan Asian countries, rest of world)
- Race group 1 (white, non-white)
- Race group 2 (white, Asian, black or African American, other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline weight group (< 60 kg, ≥ 60 kg)
- Baseline body mass index (< 22 kg/m2, ≥ 22 kg/m^2)
- Baseline vIGA-AD (moderate [vIGA-AD = 3], severe [vIGA-AD = 4])
- Baseline EASI (< 30, ≥ 30)
- Baseline EASI (≤ 21, > 21)
- Prior use of systemic therapy for the treatment of AD (yes, no)
- Prior discontinuation of systemic therapy for AD due to inadequate response or adverse reaction (yes, no)
- Prior use of biologic therapy or systemic JAK-inhibitor therapy for AD (yes, no)
- Prior discontinuation of biologic therapy or systemic JAK-inhibitor therapy for AD due to inadequate response or adverse reaction (yes, no)

Any level of a subgroup with fewer than 10% of the total population will be combined with the closest level in the same subgroup if the number of levels is more than 2.
The p-value for the treatment-by-subgroup interaction will be calculated using a logistic regression model including treatment, subgroup, treatment-by-subgroup interaction and stratification factor(s) [redacted]

Additional subgroup analyses on efficacy may be performed as deemed appropriate and necessary and will not require an amendment to the SAP.

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

5.1.1 Efficacy Endpoints

Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™)

The vIGA-AD is a validated assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 to 4: Clear = 0; Almost clear = 1; Mild = 2; Moderate = 3; and Severe = 4.

vIGA-AD 0/1 Response: Achieving vIGA-AD score 0 or 1 with at least 2-point reduction from baseline.

vIGA-AD 0 Response: Achieving a vIGA-AD score of 0 with ≥ 2 point reduction from baseline.

vIGA-AD 1 Response: Achieving a vIGA-AD score of 1 with ≥ 2 point reduction from baseline.

Revised Investigator's Global Assessment for Atopic Dermatitis (rIGA) 0/1 Response

[redacted]

Eczema Area and Severity Index (EASI)

The EASI evaluates the extent and severity of 4 key disease signs (Erythema; Induration/Papulation; Excoriation; and Lichenification) for each of the 4 body regions: Head and neck; Trunk; Upper extremities; and Lower extremities. The extent of the disease in each body region (area score $_{region)}$ is assessed based on the percentage of involvement where 0 = 0%; 1 = 1-9%; 2 = 10-29%; 3 = 30-49%; 4 = 50-69%; 5 = 70-89%; and 6 = 90-100%. The intensity score for each sign is scored as 0 = None; 1 = Mild; 1.5 = Between Mild and Moderate; 2 = Moderate; 2.5 = Between Moderate and Severe; and 3 = Severe.

The regional severity score (severity score $_{region}$) is the sum of the 4 intensity scores from the same body region: Erythema intensity $_{region}$ + Edema/Papulation intensity $_{region}$ + Excoriation intensity $_{region}$ + Lichenification intensity $_{region}$.

The regional EASI score (EASI $_{region}$) equals to the severity score $_{region}$ x area score $_{region}$ x multiplier $_{region}$, where the multiplier is 0.1 for Head and neck, 0.3 for Trunk, 0.2 for Upper extremities, and 0.4 for Lower extremities.

The total EASI score is the sum of 4 EASI $_{region}$ scores, with a range from 0 to 72. The higher the EASI score, the more severe the atopic dermatitis.

EASI 75 Response: Achieving 75% or greater improvement from baseline in EASI score

[redacted]

EASI 90 Response: Achieving 90% or greater improvement from baseline in EASI score

[redacted]

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item questionnaire with a one-week recall period that assesses the health-related quality of life of adult patients and adolescent patients aged 16 and older suffering from skin disease measuring 6 subscales: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Responses are as follows except for the question 7: “Very much”, “A lot”, “A little”, “Not at all”, and “Not relevant”. The responses are given a value from 0 to 3: Very much = 3, A lot = 2, A little = 1, Not at all = 0, Not relevant = 0. For the question 7: Yes = 3, A lot = 2, A little = 1, Not at all = 0, Not relevant = 0. For question 7a: A lot = 2, A little = 1, Not at all = 0. The DLQI score is the sum of the responses to the 10 items with a range from 0 to 30. The higher the score, the more quality of life is impaired.

Children’s Dermatology Life Quality Index (CDLQI)

The CDLQI is a 10-item questionnaire that assesses the health-related quality of life of children aged under 16 suffering from skin disease. The CDLQI measures patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week. Responses are as follows: “Very much”, “Quite A lot”, “Only A little”, and “Not at all”. The responses are given a value from 0 to 3: Very much = 3, Quite A lot = 2, Only A little = 1, Not at all = 0. Question 7a has an additional response “Prevented School” and the value corresponds to the response is 3. The CDLQI score is the sum of the responses to the 10 items with a range from 0 to 30. The higher the score, the more quality of life is impaired.

Patient Oriented Eczema Measure (POEM)

The POEM is a 7-items questionnaire that assesses disease symptoms in children and adults. Responses are as follows: “No days”, “1-2 days”, “3-4 days”, “5-6 days”, and “Every day”. The responses are given a value from 0 to 4: No days = 0, 1-2 days = 1, 3-4 days = 2, 5-6 days = 3, Every day = 4. The POEM score is the sum of the responses to the 7 items with a range from 0 to 28. If one question is left unanswered, the response of

that question is scored as 0. If more than one question is left unanswered, the questionnaire is not scored. A lower score of POEM represents a better outcome.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item self-assessment questionnaire with 7 items each for anxiety and depression subscales. Each question has 4 different choices. The responses are given a value from 0 to 3. Each subscale of anxiety and depression is the sum of the responses to the 7 items within the corresponding subscales with a range from 0 to 21. A higher subscale score is indicative of a poorer state. Categorization of each subscale score is as follows: 0 to 7 as normal, 8 to 10 as mild, 11 to 14 as moderate, and 15 to 21 as severe.

Severity Scoring of Atopic Dermatitis (SCORAD)

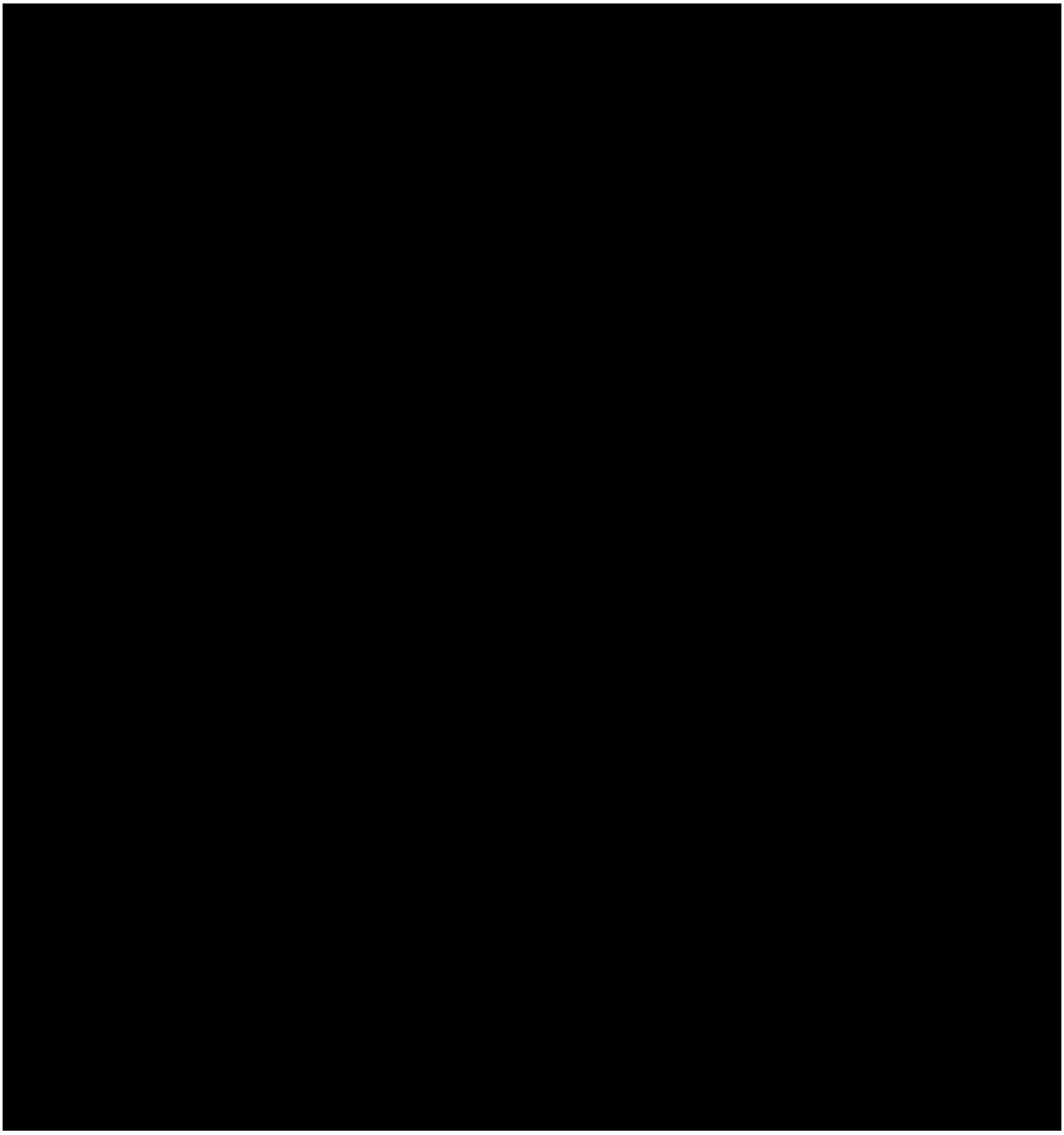
The SCORAD is a measurement tool for assessing the severity (ie, extent, intensity) of AD using both physician and patient-reported data. The SCORAD consists of three sections (A, B and C) which are then integrated in a formula to calculate the SCORAD score.

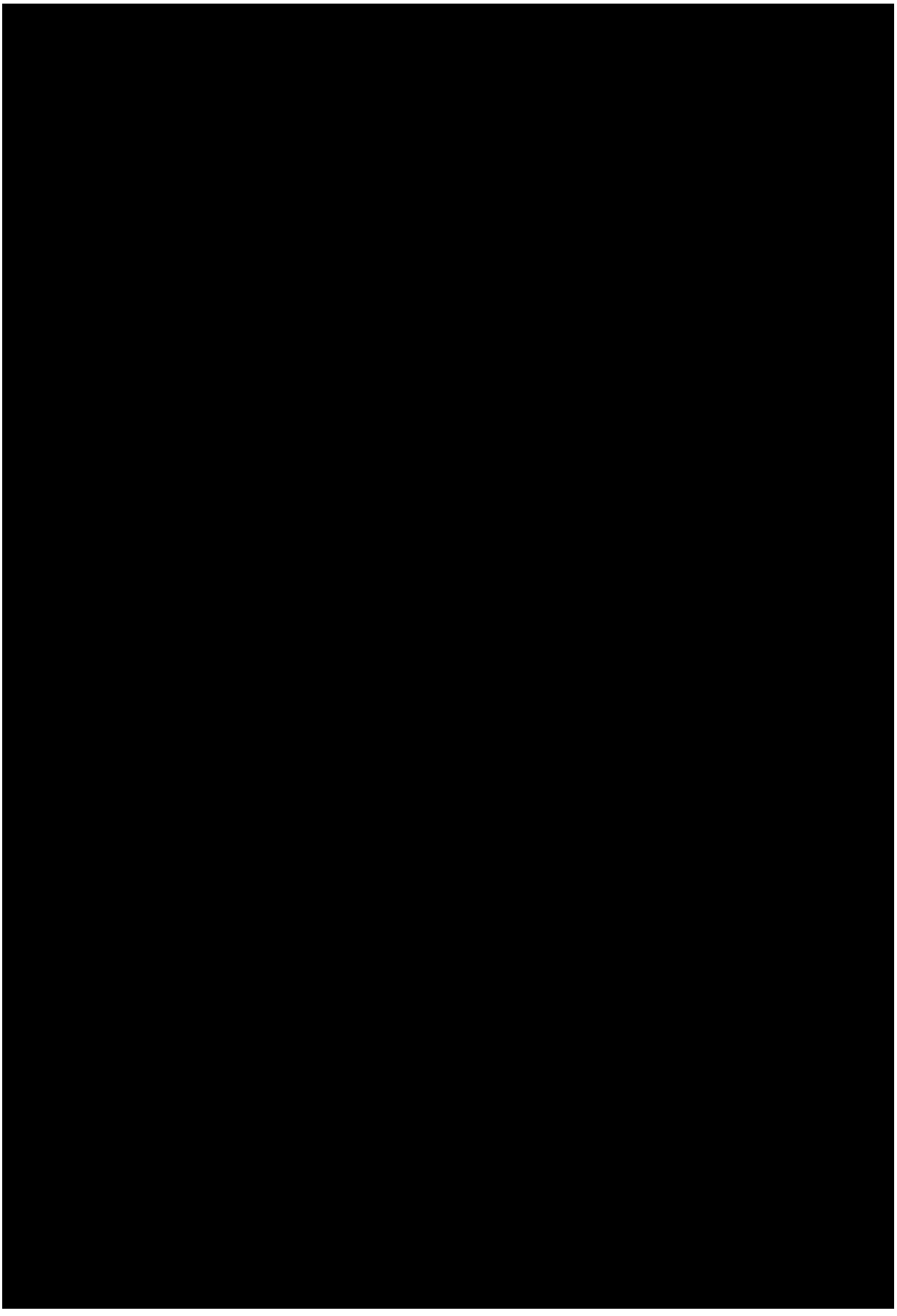
The Extent section (A) measures the body surface area affected with handprint units: Anterior Head (range from 0 to 4.5); Posterior Head (0 to 4.5); Anterior Torso (0 to 18); Posterior Torso (0 to 18); Right Anterior Arm (0 to 4.5); Left Anterior Arm (0 to 4.5); Right Posterior Arm (0 to 4.5); Left Posterior Arm (0 to 4.5); Right Anterior Leg (0 to 9); Left Anterior Leg (0 to 9); Right Posterior Leg (0 to 9); Left Posterior Leg (0 to 9); and Genitals (0 to 1). The score for this section ranges from 0 to 100, which is assigned as “A” in the SCORAD score calculation.

The Intensity section (B) assesses the intensity of the 6 clinical signs in a representative area: Erythema, Edema/Papulation, Oozing/crust, Excoriation, Lichenification, and Dryness. Each of signs is given a value from 0 to 3: Absence = 0; Mild = 1; Moderate = 2; and Severe = 3. The score of Intensity section ranges from 0 to 18 by summing the intensity score of the 6 clinical signs, which is assigned as “B” in the SCORAD score calculation.

The Patient-oriented section consists of itching and trouble sleeping. Each item will be evaluated by averaging the performances of the last 3 days or nights. A VAS is used, with 0 for no symptoms and 10 for most severe symptoms. The score for section C ranges from 0 to 20 by summing the 2 VAS scores, which is assigned as “C” in the SCORAD score calculation.

The SCORAD score is calculated as SCORAD = A/5 + 7 * B/2 + C. The maximal score of the SCORAD is 103. The higher the SCORAD score, the more severe the atopic dermatitis. The SCORAD score will be set to missing if either physician or patient assessments are missing.





[redacted]

5.1.2 Efficacy Endpoints Based on Daily Diary Data Collection

Daily diary NRS collection ends at week 52/EOT visit per protocol. Any data collected after week 52/EOT visit will be excluded from the analysis.

Worst Pruritus Numerical Rating Scale (NRS)

Worst Pruritus NRS ranges from 0 to 10, with 10 being the highest amount of itch. Patients report the severity of their worst itch over the past 24 hours in the electronic diary (eDiary).

Atopic Dermatitis Skin Pain NRS

AD skin pain NRS ranges from 0 to 10, with 10 being the highest amount of AD skin pain. Patients report the severity of their worst AD skin pain over the past 24 hours in the eDiary.

Sleep Disturbance NRS

The Sleep Disturbance NRS ranges from 0 to 10, with 10 being the highest amount of sleep disturbance. Patients report the quality of their sleep over the past 24 hours in the eDiary.

The 3 numerical rating scale (NRS) endpoints listed above will be analyzed as the weekly average score (Section 5.5).

5.1.3 Safety endpoints

Treatment-emergent Adverse Event (TEAE)

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events electronic case report form (eCRF) for AEs starting on the first dose date, and up to the End of Study (EOS) date.

Treatment-emergent Serious Adverse Events (TESAEs)

Treatment-emergent adverse events indicated as serious on the Events eCRF.

Treatment-related TEAE

A treatment-related AE is any TEAE with the relationship flag on the Events eCRF indicating there is a reasonable possibility that the event may have been caused by investigational medicinal product per investigator assessment.

TEAE Leading to Discontinuation of Investigational Product

A TEAE leading to discontinuation of investigational product is any TEAE with an action taken with investigational product indicating “Drug withdrawn” on the Events eCRF.

[redacted]

5.2 Study Dates

Informed Consent Date

The date on which subject signs the informed consent form.

Randomization Date

Randomization Date is defined as the date subject was randomized to a treatment group.

First Investigational Product Dose Date

First investigational product dose date is the date on which a subject is administered the first dose of investigational product following randomization, as recorded on the Investigational Product Administration (Double-blind) eCRF. The first investigational product dose may be the same day or after the randomization date.

Last Investigational Product Dose Date

Last investigational product dose date is the date on which a subject is administered the last dose of investigational product, as recorded on the Investigational Product Administration eCRF.

End of Investigational Product Administration Date

End of Investigational Product Administration for each subject is defined as the date when the decision was made to end investigational product, as recorded on the End of Investigational Product Administration eCRF page. This date will be used to determine the timing of permanent discontinuation of investigational product as an intercurrent event (Section 9.5.1).

Subject-level End of Study (EOS) Date

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study eCRF page.

Primary Completion Date

The primary completion date for the study is the date when the last subject across all sites has completed the assessments for week 52/EOT visit of the study.

End of Study Date

The end of study date for the study is defined as the date when the last subject across all sites has completed the assessments for the EOS/SFU visit of the study.

5.3 Study Points of Reference

Study Day 1

Study Day 1 is defined as the first investigational product dose date. For subjects who are randomized but not dosed after randomization, the Study Day 1 is defined as the date of randomization.

Maintenance Treatment Day 1

Maintenance treatment Day 1 is defined as the first blinded investigational product dose date on or after week 24. For subjects who are re-randomized but not dosed after re-randomization, the maintenance treatment Day 1 is defined as the date of re-randomization.

Open-label Treatment Day 1

Open-label treatment Day 1 is defined as the first open-label investigational product dose date on or after week 24. For subjects who are assigned to open-label but not dosed, the open-label treatment Day 1 is defined as the date of cohort assignment.

Open-label Retreatment Day 1

Open-label re-treatment Day 1 is defined as the first open-label re-treatment investigational product dose date after week 24.

Study Day

Study Day is defined as the number of days from Study Day 1.
Before Study Day 1: Study Day = (Date of Interest – Date of Study Day 1)
On or after Study Day 1: Study Day = (Date of Interest – Date of Study Day 1) + 1
Therefore, the study day prior to Study Day 1 is -1.

Baseline Assessment

Baseline assessment for the endpoint of the interest collected is defined as the last nonmissing measurement taken on or before the first dose of investigational product. In cases where baseline measurements are taken on the same day as the first dose of investigational product, it will be assumed that these measurements are taken prior to first dose of investigational product being administered except for predose vital signs, labs, PK, and ECG where the collection time of the baseline assessment must not be later than the time of the first dose of investigational product administration. For subjects who are randomized but not dosed after randomization, the baseline of the study is defined as the last nonmissing measurement prior to or on the date of randomization. In cases where the antibody measurements are taken on the same day as the first dose of rocatinlimab, the collection time of the measurement must not be later than the time of the rocatinlimab administration.

Study Period

Table 5-1 Study Period Window

Study Period	Start Time Point	End Time Point
Initiation Treatment Period	For TEAEs: Study Day 1	For TEAEs: • The day prior to the date of the first dose during maintenance or open-label treatment period (Note: TEAEs which started on the same day of the first

Study Period	Start Time Point	End Time Point
		maintenance/open-label dose date will be included in the first treatment period only if the AE start time is < the IP dose time, where the end time point for this AE of this subject will include the first maintenance/open-label dose date accordingly) • Minimum (data cutoff date, EOS date) for subjects who were not re-randomized.
	For on-treatment medications: Study Day 1	For on- treatment medications: • Week 24 date -1 if week 24 visit is available • Minimum (Week 24 target date, data cutoff date, EOS date) -1 if there is no week 24 visit. (See Table 13-1**)**
	For all other assessments: Study Day 1	For all other assessments: • Minimum (the first dose date of maintenance or open-label treatment period, data cutoff date, EOS date)
Open-label Treatment Period	For TEAE: On or after the first dose date and time of open-label treatment or the first dose date of the open-label treatment if the time part of TEAE or IP dose is missing	For TEAE: • Minimum (data cutoff date, EOS date)

Study Period	Start Time Point	End Time Point
	For on-treatment medications: OLT Day 1	For on-treatment medications: • Week 52 date if the Week 52/EOT visit date is in the week 52 analysis window. (See Table 13-1) • Minimum (Week 52 target date, data cutoff date, EOS date) if the Week 52/EOT visit date is not the week 52 analysis window. (See Table 13-1)
	For other assessments: OLT Day 1 + 1	For other assessments: • Minimum (data cutoff date, EOS date)
Maintenance Treatment Period	For TEAE: On or after the first dose date and time of maintenance treatment or the first dose date of the maintenance if the time part of TEAE or IP dose is missing	For TEAE: • Events date and time < date and time of the first dose of OLRT; if the time part of TEAE or corresponding IP dose is missing, then the TEAE will be counted toward the next treatment phase. • Minimum (data cutoff date, EOS date) for subjects who do not switch to OLRT
	For on-treatment medications: MT Day 1	For on-treatment medications: • For subjects who switch to OLRT: Date of the first open-label dose. • For subjects who do not switch to OLRT:

Study Period	Start Time Point	End Time Point
		○ Minimum (Week 52 assessment date, EOS date) if the Week 52/EOT visit date is in the week 52 analysis window. (See Table 13-1) ○ Minimum (Week 52 target date, data cutoff date, EOS date) if Week 52/EOT visit date is not in the week 52 analysis window. (See Table 13-1)
	For all other assessments: MT Day 1+1	For other assessments and on-study medications: • Date of the first open-label dose for subjects who switch to OLRT. • Minimum (data cutoff date, EOS date) for subjects who do not switch to OLRT
Open-label Retreatment Period	For TEAE: On or after the first dose date and time of open-label retreatment or the first dose date of the open-label retreatment if the time part of TEAE or IP dose is missing	For TEAE: Minimum (data cutoff date, EOS date)
	For on-treatment medications: OLRT Day 1 **+ 1**	For on-treatment medications: • Week 52 assessment date if the Week 52/EOT visit date is in the week 52 analysis window. (See Table 13-1)

Study Period	Start Time Point	End Time Point
		• Minimum (Week 52 target date, data cutoff date, EOS date) if the Week 52/EOT visit date is not the week 52 analysis window. (See Table 13-1)
	For other assessment: OLRT Day 1 +1	For other assessments: • Minimum (data cutoff date, EOS date)

5.4 Subject Disposition

Randomized

Individuals are considered randomized if they have been assigned a randomization number. Randomized individuals are referred to as “subjects”.

On-study

Subjects are considered on-study if they have been randomized and have not yet had their end of study visit.

Exposed to Investigational Product

Subjects are defined as exposed if they receive at least 1 dose of investigational product.

Completing Investigational Product

Subjects are defined as completing the investigational product if their primary reason for ending investigational product is recorded as “Completed” in the End of Investigational Product Administration eCRF.

Completing Study

Subjects are defined as completing the study if their primary reason for ending study is recorded as “Completed” in the End of Study eCRF.

5.5 Arithmetic Calculations

Duration of Investigational Product Exposure (Days)

For Initiation Treatment Period:

- Exposure Duration (Days) = Minimum (last dose date in the initiation treatment period + 27, the first dose date of maintenance or open-label treatment period - 1, EOS date) – first dose date of initiation treatment period+ 1

For Open-label Treatment Period:

- Exposure Duration (Days) = Minimum (last dose date in the open-label treatment period + 27, EOS date) – first dose date of open-label treatment period + 1

For Maintenance Treatment Period:

- Exposure Duration (Days) = Minimum (last dose in the maintenance treatment period + 27, date of first open-label dose for subjects who switch to open-label retreatment – 1, EOS date) - first dose date of maintenance period + 1

For Open-label Retreatment Period:

- Exposure Duration (Days) = Minimum [last dose date in the open-label retreatment period + 27, EOS date] - first dose date of open-label retreatment period + 1

Duration of AD

The number of years from the diagnosis date (DXDT) of AD to the date informed consent is signed.

Observed Portion	Missing Portion	Duration of Migraine (Years)
Year, Month, Day	NA	(Informed Consent Date – DXDT+1) / 365.25
Year, Month	Day	[Year (Informed Consent Date) – Year(DXDT)] + [Month(Informed Consent Date) – Month(DXDT)] / 12 [a]
Year	Month, Day	[Year (Informed Consent Date) – Year(DXDT)] [a]

[a] If it equals 0, add 1/12 years (ie, 1 month) to avoid a disease duration of 0. If the final derived duration of AD is greater than the reported age, the duration of AD will be set to age.

Age at AD Disease Onset

Age at baseline - Duration of AD

Weekly Average Score of Daily NRS

The 3 numerical rating scales (NRS) listed in Section 5.1.2 will be analyzed as the weekly average score based on the weekly analysis window in Appendix D. Weekly

average score is the sum of the observed daily NRS scores divided by the number of observed daily NRS scores in each weekly window if there are at least 3 days with observed daily NRS. Otherwise, the weekly average score will be set to missing.

Another set of weekly averages requiring at least 4 days with observed daily NRS scores in each weekly window will also be derived to support a sensitivity analysis for the endpoints with respect to achieving ≥ 4-point reduction from baseline in weekly average of daily NRS scores during initiation treatment period.

Change From Baseline

Postbaseline monthly value – Baseline value, as defined in Section 5.3.

If the baseline or postbaseline value is missing, the change from baseline value will be set to missing.

Percent Change From Baseline

The change from baseline divided by baseline and multiplied by 100:

(Postbaseline value – Baseline value) * 100 / Baseline value

If the baseline value is 0 and the postbaseline value is also 0, the percent change from baseline is set to 0. If the baseline value is 0 and the postbaseline value is non-zero, the percent change from baseline is set to missing.

Time to Initiation of Rescue Therapy for AD

The observation period for rescue therapy for AD during each treatment period is

defined in Table 5-1.

Time to initiation of rescue therapy for AD during initiation treatment period will be calculated as follows:

- Time (days) = Date of first use rescue therapy for AD – study day 1 date + 1

Time to initiation of rescue therapy for AD during maintenance treatment period will be calculated as follows:

- Time (days) = Date of first use rescue therapy for AD – maintenance treatment day 1 date + 1

Subject Incidence

The subject incidence for a given event is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects (i.e., number of

at-risk subjects). For subjects with multiple occurrences of the same event will only be counted once.

Total Subjects-years at Risk (for Exposure-adjusted Subject Incidence Rate)

Time at risk for each subject will differ for each AE. Please refer to the Table 5-1 to calculate time at risk (in days) in each study period for each subject for subjects without events. For subjects with events, only the time up to the first event contributes to the total subject-years at risk. The time at risk in days will be summed over all subjects by treatment group and then be converted to subject-years at risk, as the number of days at risk / 365.25.

Exposure-Adjusted Subject Incidence Rate

The exposure-adjusted subject incidence rate for a given event is defined as the number of subjects with at least one reported occurrence of the event in a given study period (refer to Table 5-1) divided by total subject-years at risk. This rate will be presented per 100 subject-years. For subjects with multiple occurrences of the same event, the event will be only counted once per subject in each study period.

Exposure-adjusted subject incidence rate = (100 * total number of subjects with TEAE) / total subject-years at risk.

6. Analysis Sets

6.1 Initiation Treatment Period (Day 1 Through Week 24)

6.1.1 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects. Subjects will be analyzed according to the initial randomized treatment. Analyses of disposition, demographic and baseline data, Important Protocol Deviations (IPDs), efficacy endpoints during the initiation treatment period will utilize this analysis set.

6.1.2 Safety Analysis Set

The safety analysis set includes all subjects who receive at least 1 dose of investigational product. Subjects will be analyzed according to the actual treatment received, where subjects who received the highest dose of rocatinlimab will be analyzed in the corresponding rocatinlimab treatment group regardless of the randomized treatment. Analyses of safety endpoints and summary of investigational product administration will utilize this analysis set.

6.2 Post Week 24

6.2.1 Maintenance Treatment Period

6.2.1.1 Full Analysis Set

The full analysis set (FAS) includes all rerandomized subjects. Subjects will be analyzed according to the rerandomized treatment. Analyses of disposition and efficacy endpoints during maintenance treatment period will utilize this analysis set.

6.2.1.2 Safety Analysis Set

Subjects who are rerandomized at week 24 and receive at least 1 dose of investigational product during the maintenance treatment period. Subjects will be analyzed according to the **randomized and rerandomized** treatment.

6.2.2 Open-label Treatment Period

6.2.2.1 Full Analysis Set

Subjects who switch to open-label treatment period at week 24.

6.2.2.2 Efficacy Analysis Set / Safety Analysis Set

Subjects who switch to open-label treatment period at week 24 and receive at least 1 dose of open-label rocatinlimab 300 mg. **Safety data will be summarized by initial randomized treatment.**

6.2.3 Open-label Retreatment Period

6.2.3.1 Efficacy Analysis Set / Safety Analysis Set

Subjects who switch to open-label retreatment period from blinded maintenance treatment and receive at least 1 dose of open-label rocatinlimab 300 mg. **Safety data will be summarized by randomized and rerandomized treatment**.

6.3 Entire Study

6.3.1 Safety Analysis Set

The safety analysis set includes all subjects who receive at least 1 dose of investigational product during the study, which is equivalent to the safety analysis set for the initiation treatment period (Section 6.1). Subjects will be analyzed based on the assigned treatment in each treatment period (i.e. the initial randomized treatment for the initial treatment period, the rerandomized treatment for the maintenance treatment period, and assigned treatment for the open-label treatment and open-label retreatment period) by the following treatment groups:

- **Placebo**
- **All Rocatinlimab 150 mg (Q4W and Q8W combined)**

- **All Rocatinlimab 300 mg (Q4W and Q8W combined)**
- **All Rocatinlimab**

7. Planned Analyses

Subjects in monotherapy cohort and combination therapy cohort will be combined for the primary comparison. When appropriate, the endpoints will be summarized descriptively within each monotherapy cohort or combination therapy cohort.

7.1 Interim Analysis and Early Stopping Guidelines

No formal interim analysis will be performed in this study.

7.2 Primary Analysis

The primary analysis will be conducted when all subjects have completed the week 52/EOT visit, and the available data have been entered, cleaned, and locked. The objective of the primary analysis is to assess complete efficacy and safety data through week 52 and additional safety data available during SFU as of the data cutoff date.

7.3 Final Analysis

The final analysis will be conducted at the end of the study when all subjects have completed the EOS visit, and the available data have been entered, cleaned, and locked. The objective of the final analysis is to assess complete safety data through EOS on all subjects over the entire study period.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database, eCOA data, [redacted], antibody, ECG and central laboratory data. The database will be subjected to edit checks outlined in the Data Management Plan (DMP). Additional details will be provided in the DMP and Data Acquisition Requirements Specification (DARS).

8.3 Handling of Missing and Incomplete Data

Missing data could occur due to missed visits/assessments intermittently or early discontinuation from study.

Missing data in efficacy endpoints will be imputed using methods specified in Section 9.5.2.

Missing assessments in safety endpoints will not be imputed.

Any laboratory value below the lower limit of quantification or above the upper limit of the quantification will be imputed using the respective limit of quantification for analysis. Any anti-rocatinlimab antibody assessments below the lower limit of quantification will be imputed using the respective limit of quantification for analysis. For any PK concentration below the lower limit of quantification, a value of zero will be used in the analysis.

Missing and incomplete dates in AE and concomitant medication will be imputed as outlined in Appendix C.

8.4 Detection of Bias

This study has been designed to minimize potential bias by allocating treatment groups randomly, assessing endpoints and handling withdrawals without knowledge of the treatment. Other factors that may bias the results of the study include:

- Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- Inadvertent breaking of the blind before formal unblinding
- Investigational product dosing non-compliance
- The timing of and reasons for early withdrawal from treatment and from study

The incidence of these factors may be assessed. Important protocol deviations will be listed and/or tabulated in the clinical study report (CSR). If necessary, the incidence of other factors will be tabulated.

Any breaking of the blind for individual subjects prior to formal unblinding of the study will be documented in the CSR.

The timing of and reasons for early withdrawal from treatment and from study will be tabulated and/or listed.

8.5 Outliers

Histograms will be examined to identify outliers in any of the continuous variables used in the analyses. Unexpected and/or unexplained values in categorical data will be identified by utilizing frequency tables.

Outliers due to data entry errors will be corrected by the study team before final database lock. The validity of any questionable values or outliers will be confirmed.

Outliers or any questionable values with confirmed validity will be included in the analyses presented in this statistical analysis plan unless there is sufficient justification to exclude them. However, ad-hoc sensitivity analyses may be conducted to evaluate the influence of extreme values in the data.

8.6 Distributional Characteristics

Continuous endpoints of change or percent change from baseline value will be analyzed under normality assumption. Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required, data transformation or alternative non-parametric methods of analyses will be utilized.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Datasets, tables, figures, and listings will be produced and validated in accordance with SOP-430399. Standard macros will be used when available.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively by the randomized treatment. For categorical endpoints, the descriptive statistics will contain frequency, percentage, and corresponding Clopper-Pearson 95% confidence interval (CI) where appropriate. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard error, standard deviation, median, first quartile, third quartile, minimum, and maximum.

Endpoints defined at week 24 or earlier will be assessed between rocatinlimab 300 mg and placebo, and between rocatinlimab 150 mg and placebo. Endpoints defined after week 24 will be summarized descriptively based on the treatment received during the 28-week maintenance treatment period and the open-label treatment period.

[redacted]

[redacted]

9.2 Subject Accountability

The number and percentage of subjects who were randomized, received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing will be summarized during each treatment period.

The number and percentage of subjects completed study, discontinued study and reasons for discontinuing will the summarized during the entire study period.

Key study dates for the first subject enrolled, last subject enrolled, last subject's end of Investigational product and last subject’s end of study will be presented.

The number and percentage of subjects randomized will be tabulated by study site.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject’s initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

The final IPD list will be used to produce the Summary of IPDs table and the list of subjects with IPDs.

9.4 Demographic and Baseline Characteristics

Demographic and baseline disease characteristics including medical history and prior AD treatments will be summarized using descriptive statistics by randomized treatment group and overall using FAS for initiation treatment, maintenance treatment period and open-label treatment period. If multiple races have been reported for a subject, the subject will be categorized as multiple races.

The following demographic and baseline characteristics will be summarized but not limited to:

- Age (years)
- Sex
- Ethnicity

- Race
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI, kg/m^2)
- Stratification factors (monotherapy vs. combination therapy, severity of disease and geographical region)
- Medical history

- Selected clinical outcome assessment (COA)/patient-reported outcome (PRO) at baseline

9.5 Efficacy Analyses

9.5.1 Primary and Supportive Estimands

The estimands for initiation treatment period and maintenance treatment period will be defined separately to address different clinical questions of interest and intercurrent events for different treatment periods.

9.5.1.1 Primary and Supportive Estimands during Initiation Treatment Period

There will be three estimands addressing different clinical questions of interest and intercurrent events for initiation treatment period. Two intercurrent events will be considered to estimate the treatment effects: initiation of rescue therapy for AD (Appendix B) and permanent discontinuation of investigational product without rescue therapy for AD. Subjects who permanently discontinue investigational product for any reason before week 24 are encouraged to complete all remaining study visits and procedures through week 24 for evaluation of endpoints, with the exception of investigational product administration and post-dose monitoring procedures.

The following primary and supportive estimands will be implemented to handle intercurrent events during initiation treatment period specifically according to the clinical questions of interest.

9.5.1.1.1 Primary Estimand

The primary estimand for a binary endpoint (Section 2.1) is to measure the effect of rocatinlimab as assessed by the difference in response rates between each of the 2 rocatinlimab treatment groups (300 mg and 150 mg) and placebo among randomized subjects within moderate-to-severe AD population without rescue therapy for AD, regardless of permanent discontinuation of investigational product. Subjects initiating rescue therapy for AD will be classified as nonresponders at all subsequent time points on or before week 24 (composite strategy reflecting lack of response). For subjects who do not use rescue therapy for AD, but permanently discontinue investigational product, data retrieved after permanent discontinuation of investigational product will be included as collected (treatment policy strategy).

The primary estimand for a continuous endpoint (Section 2.1) is to measure the effect of rocatinlimab as assessed by the difference in means of change or percent change from baseline value between each of the 2 rocatinlimab treatment groups (300 mg and 150 mg) and placebo among randomized subjects within moderate-to-severe AD population without rescue therapy for AD, regardless of permanent discontinuation of investigational product. Subjects initiating rescue therapy for AD will be included in the analysis, and each subject's worst observation, including baseline value, before initiation of rescue therapy for AD will be carried forward (WOCF) to all subsequent time points on for before week 24 (composite strategy reflecting lack of response). For subjects who do not use rescue therapy for AD but permanently discontinue investigational product, data retrieved after permanent discontinuation of investigational product will be included as collected (treatment policy strategy).

The primary estimand overall endorses a hybrid strategy since different strategies are implemented for the 2 intercurrent events.

9.5.1.1.2 Supportive Estimand 1

The supportive estimand 1 for the selected binary endpoints is to measure the effect of rocatinlimab as assessed by the difference in response rates between each of the 2 rocatinlimab treatment groups (300 mg and 150 mg) and placebo among randomized subjects where subjects who initiate rescue therapy for AD or discontinue investigational product permanently are considered treatment failures and will be classified as nonresponders at all subsequent time points on or before week 24 after the intercurrent events (composite strategy reflecting lack of response).

9.5.1.1.3 Supportive Estimand 2

The supportive estimand 2 for the selected endpoints is to measure the effect of rocatinlimab as assessed by the difference in response rates (binary endpoints), and by the difference in means of change or percent change from baseline value (continuous endpoints) between each of the 2 rocatinlimab treatment groups (300 mg and 150 mg) and placebo among randomized subjects regardless of rescue therapy for AD or permanent discontinuation of investigational product. Data retrieved after rescue therapy initiation or permanent discontinuation of investigational product will be included as collected (treatment policy strategy).

Table 9-1 Primary and Supportive Estimands During Initiation Treatment Period

Endpoint Type	Estimand	Intercurrent Events	
		Rescue Therapy Initiation for AD	Permanent IP Discontinuation
Binary	Primary estimand (Hybrid)	Composite strategy: • Set to Nonresponder	Treatment policy strategy: • Keep observed data
	Supportive estimand 1 (Composite)	Composite strategy: • Set to Nonresponder	Composite strategy: • Set to Nonresponder
	Supportive estimand 2 (Treatment policy)	Treatment policy strategy: • Keep observed data	Treatment policy strategy: • Keep observed data
Continuous	Primary estimand (Hybrid)	Composite strategy: • WOCF	Treatment policy strategy: • Keep observed data
	Supportive estimand 2 (Treatment policy)	Treatment policy strategy: Keep observed data	Treatment policy strategy: Keep observed data

For composite strategy implementation in endpoints collected at each visit, assessments after the day of intercurrent event, corresponding to either rescue therapy start date or end of investigational product administration date, will be set to nonresponse for binary endpoints (or WOCF for continuous endpoints); for weekly endpoints derived from daily diaries, the week when the intercurrent event occurred and thereafter will be set to nonresponse for binary endpoints (or WOCF for continuous endpoints).

9.5.1.2 Primary Estimand and Supportive Estimand for Maintenance Treatment Period

Five intercurrent events (ICEs) will be considered to estimate the maintenance of response during the blinded maintenance treatment period:

1. Initiation of rescue therapy for AD (Appendix B)

2. Switch to open-label retreatment after meeting the relapse criterion for the endpoint of interest
3. Permanent discontinuation of investigational product requested by the subject due to lack of efficacy
4. Switch to open-label retreatment without meeting the relapse criterion for the endpoint of interest
5. Permanent discontinuation of investigational product for reasons other than lack of efficacy as requested by the subject

The above ICEs will be handled differently in each estimand as specified in Table 9-2.

9.5.1.2.1 Maintenance Primary Estimand (Hybrid)

The maintenance primary estimand is to estimate the maintenance treatment effect of rocatinlimab among subjects achieving response at week 24 in each of the four rocatinlimab treatment groups (300 mg Q4W, 300 mg Q8W, 150 mg Q4W, and 150 mg Q8W), as well as placebo. Maintenance response is defined as response without rescue therapy for AD, moving to open-label retreatment upon **meeting the** relapse **criterion for the endpoint of interest** or permanent discontinuation of IP due to lack of efficacy (composite **strategy for ICEs 1 to 3 above)**, **regardless of whether the 2 remaining** ICEs listed above **have occurred or not (treatment policy strategy)**. Under composite strategy, subjects will be classified as nonresponders for binary endpoints, each subject's baseline value will be carried forward (BOCF) for continuous endpoints (composite strategy reflecting lack of response) at all subsequent time points **during the maintenance treatment period** after the occurrence of the ICE. Under **treatment policy strategy, data retrieved after the occurrence of the ICEs will be included as collected**.

The primary estimand overall endorses a hybrid strategy since different strategies are implemented for multiple intercurrent events.

9.5.1.2.1 Maintenance Supportive Estimand (Hypothetical)

The maintenance supportive estimand is used to analyze exploratory endpoints during maintenance treatment period, where all ICEs were handled using hypothetical strategy. The treatment effect under a hypothetical strategy is estimated as if rescue therapy for AD, switching to open-label retreatment, or permanent discontinuation of investigational product due to any reason did not occur. Data will be set to missing at all subsequent time points after the occurrence of the ICEs.

Table 9-2 Primary and Supportive Estimand During Maintenance Treatment Period

Estimand	Analysis Strategy for Intercurrent Events				
	Initiation of rescue therapy for AD	Switch to open-label retreatment without rescue therapy		Permanent discontinuation of investigational product without rescue therapy	
		Meeting relapse criteria[a]	Not meeting relapse criteria[a]	Due to lack of efficacy per subject request	Due to any other reasons
Maintenance Primary Estimand for Binary Endpoints (Hybrid)	Composite: Set to NRI	Composite: Set to NRI	**Treatment Policy: Keep Observed Data**	Composite: Set to NRI	**Treatment Policy: Keep Observed Data**
Maintenance Primary Estimand for Continuous Endpoints (Hybrid)	Composite: Set to study baseline	Composite: Set to study baseline	**Treatment Policy: Keep Observed Data**	Composite: Set to study baseline	**Treatment Policy: Keep Observed Data**
Maintenance Supportive Estimand for Binary and Continuous Endpoints (Hypothetical)	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing

[redacted]

9.5.2 Missing Data Imputation Methods(s)

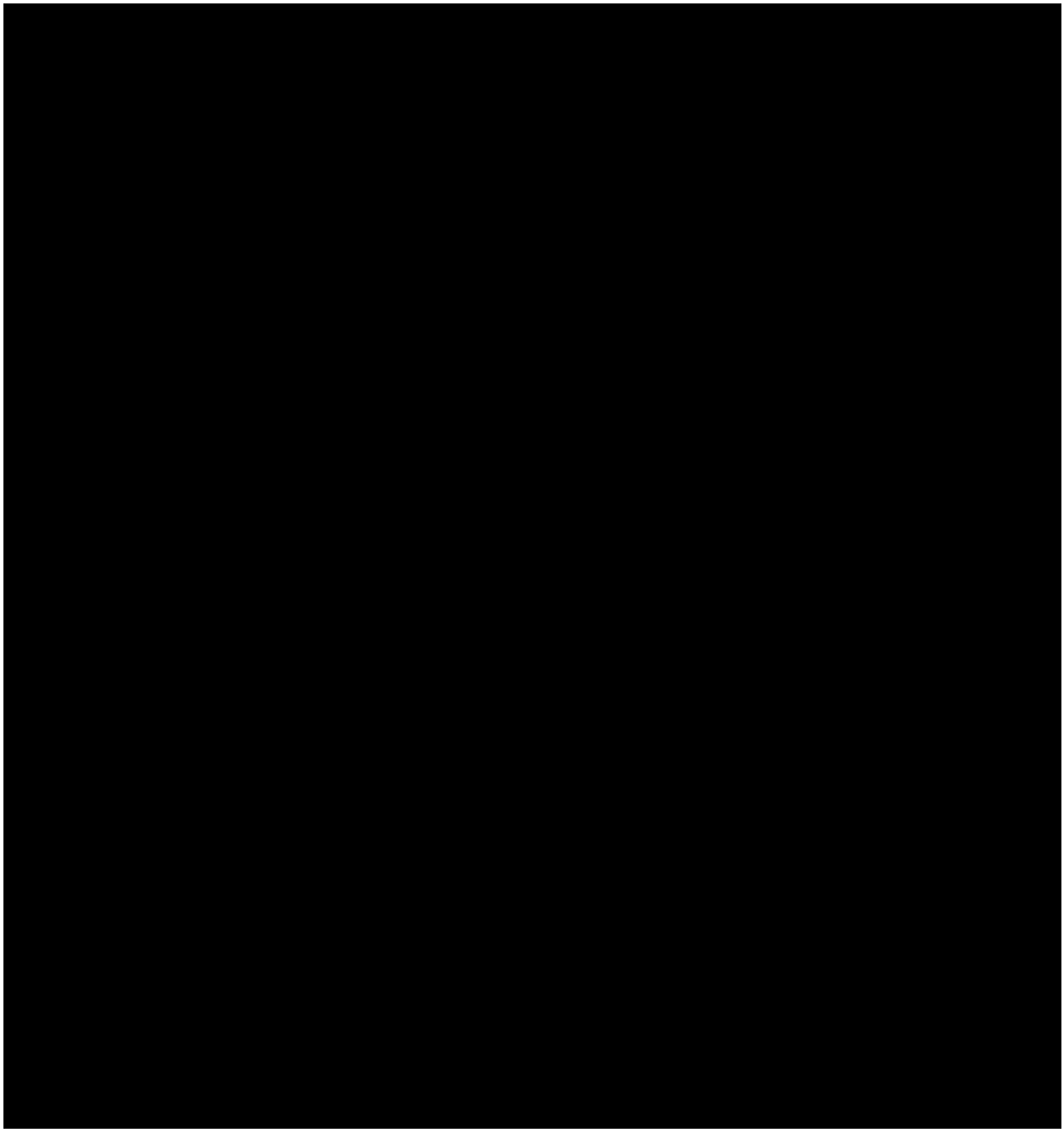
Remaining missing data after applying the strategy for each intercurrent event will be imputed separately for initiation treatment period and maintenance treatment period, using methods specified below.

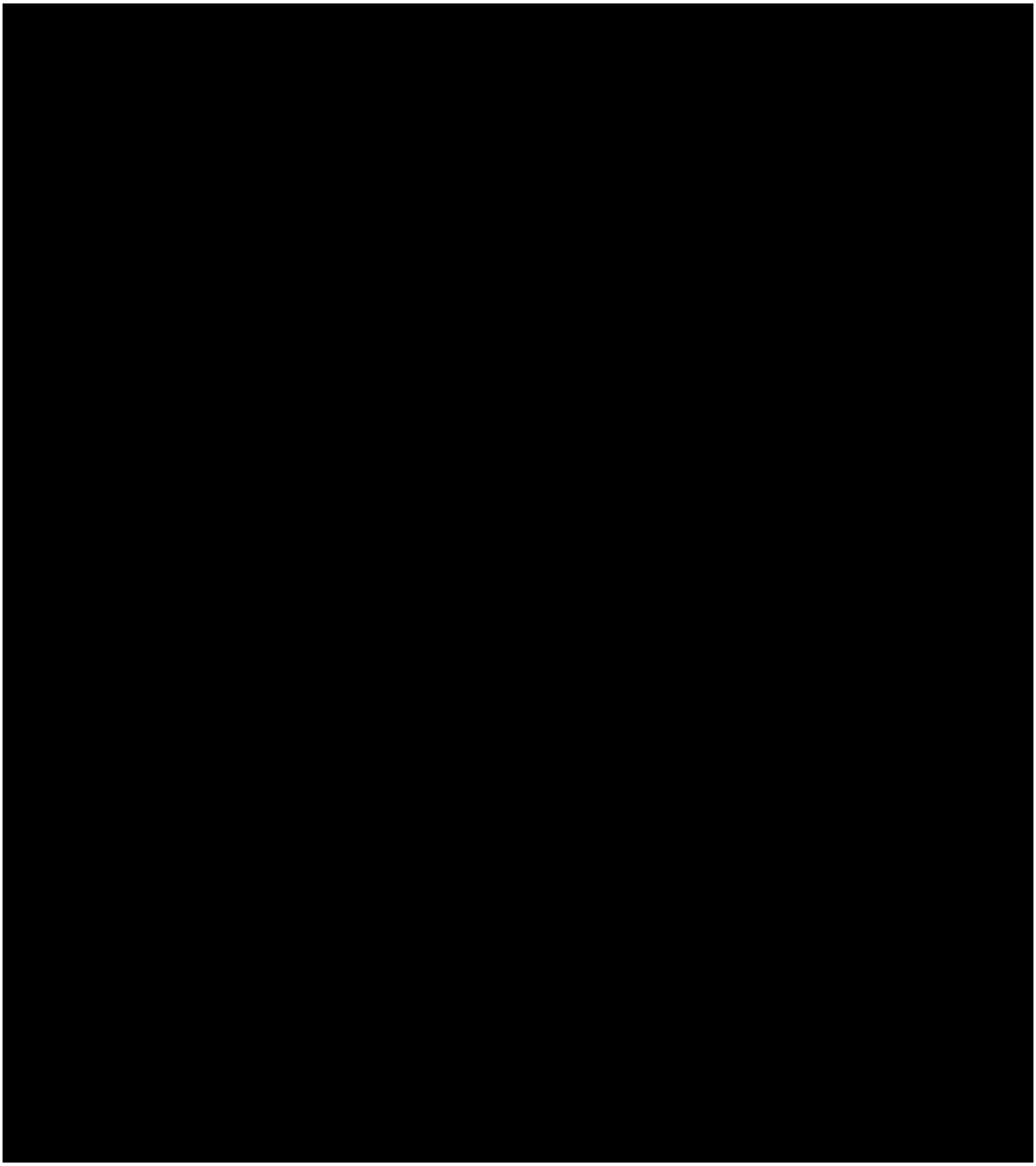
9.5.2.1 Nonresponder Imputation (NRI)

Missing data in binary endpoints will be imputed as nonresponder during initiation treatment period. The NRI imputation will be the primary method of handling missing binary data during initiation treatment period.

9.5.2.2 Last Observation Carried Forward (LOCF)

During maintenance treatment period, last observation carried forward (LOCF) imputation will be used to impute remaining missing data after the maintenance supportive estimand (hypothetical) handling, **including data starting at week 24**.





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9.5.3 Analysis method

9.5.3.1 Cochran-Mantel-Haenszel (CMH) Test

Mantel-Haenszel common risk difference between each rocatinlimab treatment group and placebo, the corresponding 95% confidence interval (CI) based on Klingenberg confidence limits will be provided adjusting for randomization strata. Treatment comparisons of binary efficacy endpoints will be based on CMH test stratified by the randomization strata. The CMH p-value will be reported.

9.5.3.2 Analysis of Covariance (ANCOVA)

Treatment comparisons of continuous efficacy endpoints will be based on analysis of covariance (ANCOVA) model including treatment, randomization strata, and relevant baseline value as covariates. The least squares (LS) mean for each treatment group, the difference in LS means between each rocatinlimab treatment group and placebo, standard error, p-value, and 95% CI, unless otherwise specified, will be provided.

9.5.3.3 Time to Initiation of Rescue Therapy

The cumulative percentage of subjects who initiated rescue therapy for AD will be provided by each treatment group descriptively during initiation treatment period and maintenance treatment period, separately.

9.5.4 Analysis of Primary Efficacy Endpoint(s)/Estimand(s)

Unless otherwise specified, efficacy analyses will be conducted on the full analysis set defined in Section 6.1. The primary and sensitivity analyses of the coprimary endpoints are listed in Table 9-4. Nominal p-values from the primary analysis will be provided for each treatment comparison and statistical significance will be determined based on the

[redacted]

Table 9-4 Summary of Coprimary Endpoints Analysis

Endpoint	Analysis Type	Estimand	[redacted]	Analysis Method
• vIGA 0/1 at W24 (for ex-US submission) • rIGA 0/1 at W24 (for US submission) • EASI 75 at W24 (for both ex-US and US submissions)	Primary analysis	Primary estimand (hybrid)		CMH
	Sensitivity analysis	Primary estimand (hybrid)		CMH
		Supportive estimand 1 (composite)		
		Supportive estimand 2 (treatment policy)		
	Subgroup analyses (Section 4.2)	Primary estimand (hybrid)		CMH

9.5.5 Analysis of Selected Secondary Efficacy Endpoint(s)/Estimand(s)

The primary and sensitivity analyses of selected secondary endpoints are listed in Table 9-5.

Table 9-5 Summary of Selected Secondary Endpoints Analysis Included in Graphical Testing Hierarchy

Endpoint	Analysis Type	Estimand	[redacted]	Analysis Method
• vIGA-AD 0/1 at W24 (for US submission) • EASI 75 at W16 • vIGA 0/1 at W16 • ≥ 4-point reduction in weekly average of daily worst pruritus NRS at W24 • ≥ 4-point reduction in weekly average of daily worst pruritus NRS at W16 • EASI 90 at W24 • ≥ 4-point reduction in weekly average of daily AD skin pain NRS at W24	Primary analysis	Primary estimand (hybrid)		CMH
	Sensitivity analysis	Primary estimand (hybrid)		CMH
		Supportive estimand 1 (composite)		
		Supportive estimand 2 (treatment policy)		
• Change in CDLQI at W24 (for Ex-US submission)	Primary analysis	Primary estimand (hybrid)		ANCOVA
	Sensitivity analysis	Primary estimand (hybrid)		
		Supportive estimand 2 (treatment policy)		

9.5.6 Analysis of Other Secondary and Exploratory Efficacy Endpoint(s)/Estimand(s) During Initiation Treatment Period

Initiation Treatment period: The primary analysis of other secondary and exploratory endpoints during initiation treatment period are listed in Table 9-6. There is no sensitivity analysis planned for these endpoints. For the other secondary and exploratory efficacy

endpoints, nominal p-values will be provided without multiplicity control for the comparison between each treatment group and placebo.

Table 9-6 Summary of Other Secondary and Exploratory Endpoints Analysis During Initiation Treatment Period

Endpoint	Analysis Type	Estimand	[redacted]	Analysis Method
Binary efficacy endpoints (other secondary/exploratory endpoints)	Primary analysis	Primary estimand (hybrid)		CMH
	Sensitivity analysis	Supportive estimand 2 (treatment policy)		
Continuous efficacy endpoints	Primary analysis	Primary estimand (hybrid)		ANCOVA
	Sensitivity analysis	Supportive estimand 2 (treatment policy)		

9.5.7 Analysis of Exploratory Efficacy Endpoint During Maintenance Treatment Period

The primary analysis of exploratory endpoints during maintenance treatment period are listed in Table 9-7.

Table 9-7 Summary of Other Secondary and Exploratory Endpoints Analysis During Maintenance Treatment Period

Endpoint		Estimand	[redacted]	Analysis Method
Binary efficacy endpoints	vIGA-AD, EASI, Worst Pruritus NRS, AD skin pain NRS, DLQI related endpoints	Maintenance primary estimand (hybrid)		Descriptive
	Remaining binary endpoints	Maintenance supportive estimand (hypothetical)		Descriptive
Continuous efficacy endpoints	vIGA-AD, EASI, Worst Pruritus NRS, AD skin pain NRS, DLQI/CDLQI related endpoints	Maintenance primary estimand (hybrid)		Descriptive
	Remaining continuous endpoints	Maintenance supportive estimand (hypothetical)		Descriptive

9.5.8 Analysis of Exploratory Efficacy Endpoint(s) for Open-label and Open-label Re-treatment Periods

Efficacy endpoints of open-label treatment cohort and open-label retreatment cohort will be analyzed separately. Efficacy data after initiation of systemic rescue for AD (including

Topical JAK inhibitors) or permanent discontinuation of IP due to lack of efficacy or protocol specified criteria (open-label stopping rule) will be set to missing. Data will be summarized descriptively without data imputation for the remaining missing data.

9.6 Safety Analyses

Safety Data will be summarized separately by treatment periods, **as well as for the entire study.** (refer to Section 6).

Pooled safety data including TEAEs and EOIs **during the entire study** will be summarized based on **assigned** treatment at the time of event onset. Safety data from the open-label treatment or retreatment periods will be attributed to the rocatinlimab 300 mg regardless of the previous treatment received.

9.6.1 Analyses of Primary Safety Endpoint(s)

Not applicable.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 28.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

Subject incidence (frequency) and incidence rate of all TEAE, TESAE, TEAE leading to discontinuation of investigational product, treatment related TEAE will be tabulated by preferred term in descending order of the incidence rate.

Summary of all TEAE will be tabulated by system organ class in alphabetical order and by preferred term in descending order of the incidence rate.

Summaries of all TEAE and TESAE will be tabulated by system organ class, preferred term, and severity grade.

Adverse event of interest (EOI: Appendix F) will include but not be limited to infections, injection-related reactions, injection site reactions, hypersensitivity reactions, **anaphylactic reactions,** major adverse cardiovascular events (MACE), malignancy, neuropsychiatric events, aphthous ulcers, conjunctivitis, and gastrointestinal ulceration/perforation.

Subject incidence (frequency) and incidence rate of EOI (standardized MedDRA queries and/or Amgen Medical Queries) will also be summarized according to their categories and preferred terms.

Unadjusted subject incidence rates will be summarized for initiation treatment period; exposure-adjusted subject incidence rates will also be summarized during treatment period after week 24, and during the entire study.

9.6.3 Laboratory Test Results

The following analyses will be provided for chemistry and hematology laboratory data:

- Summary statistics over time of selected laboratory data by treatment group
- Shifts in grades of selected safety laboratory values, based on common terminology criteria for adverse events (CTCAE) grade (version 5.0), between baseline and the worst on-study value will be tabulated by treatment group, as applicable
- Summary of grades ≥ 3 laboratory toxicities for selected laboratory parameters, as applicable
- Subject incidence of suspected Hy's law cases
- Summary of liver function abnormalities for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL) or the following categories:
  - ALT (> 3x upper limit of normal (ULN); > 5x ULN; > 10x ULN; > 20x ULN respectively)
  - AST (> 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN respectively)
  - AST or ALT (> 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN respectively)
  - Total Bilirubin (> 1x ULN; > 1.5x ULN; > 2x ULN respectively) and ALP (> 1.5 ULN)

9.6.4 Vital Signs

The analyses of vital signs will include summary statistics over time by treatment group only during the initiation treatment period. Subject incidence of the following defined categories for systolic/diastolic blood pressure (SBP/DBP) and heart rate (HR) will be provided:

- Increase from baseline ≥ 20 mmHg in SBP with SBP > 140 mmHg
- Increase from baseline ≥ 20 mmHg in SBP with SBP ≤ 140 mmHg
- Increase from baseline ≥ 10 mmHg in DBP with DBP > 90 mmHg
- Increase from baseline ≥ 10 mmHg in DBP with DBP ≤ 90 mmHg

- Change from baseline in HR of ≥ 15 bpm (increase) or HR ≥ 120 bpm
- Change from baseline in HR of ≤ -15 bpm (decrease) or HR ≤ 50 bpm

9.6.5 Physical Measurements

The analysis of physical measurements will include summary statistics **over time** by treatment group.

9.6.6 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

Shift in ECG diagnosis/interpretation between baseline and postbaseline will be summarized.

[redacted]

9.6.8 Tanner Staging

The self-assessment of tanner staging for pubertal maturation at baseline and postbaseline visits will be summarized by gender and treatment group.

[redacted]

9.6.10 Exposure to Investigational Product

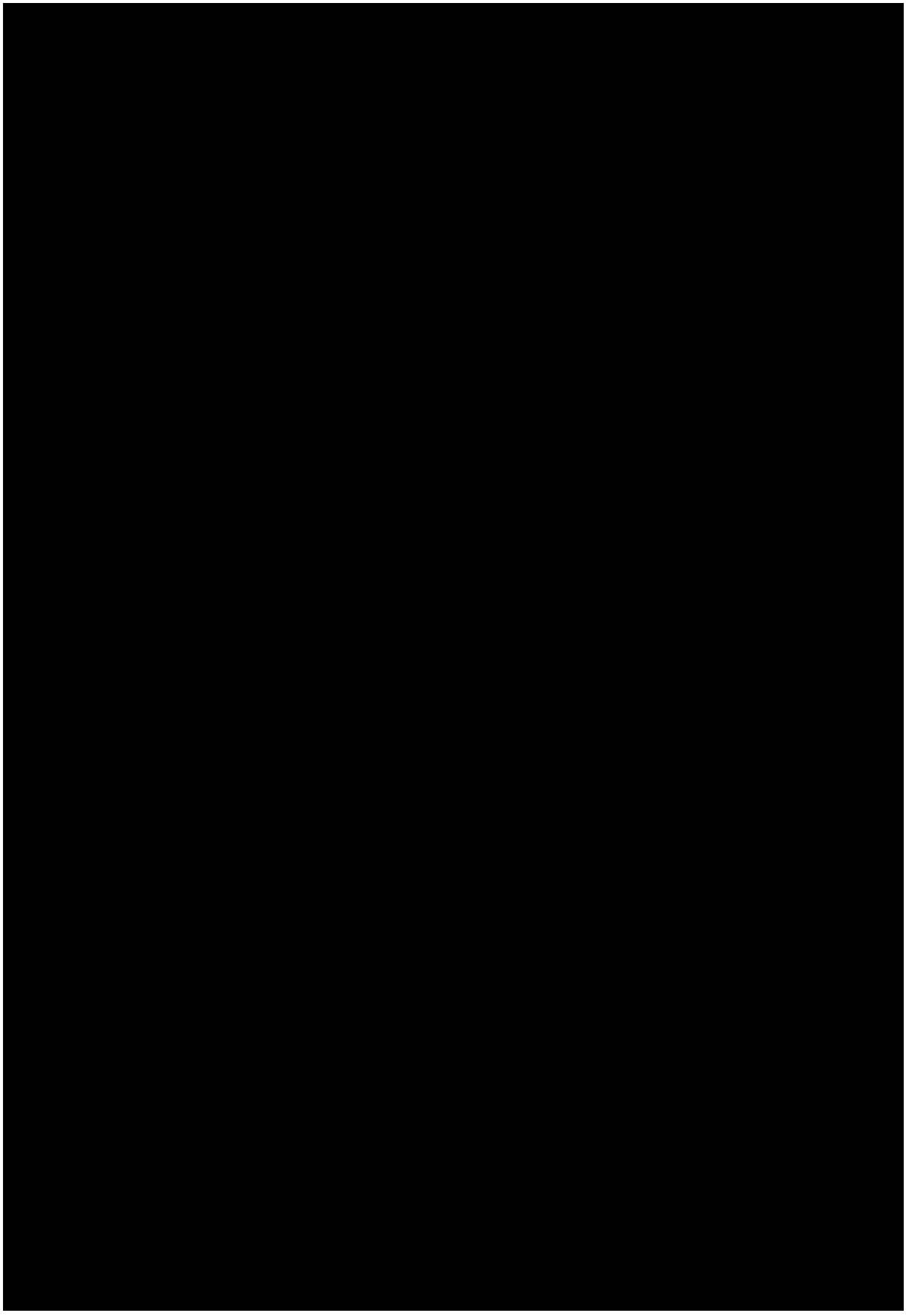
Descriptive statistics will be produced to describe the exposure to investigational product by treatment period and group.

9.6.11 Exposure to Concomitant Medication

Number and percentage of subjects receiving rescue therapy will be summarized by medication of interest category for each treatment group. See Appendix B for a list of selected medications and their groupings.

9.7 Other Analyses

[redacted]



[redacted]

11. Literature Citations / References

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National Institute of Health and care Excellence Decision Support Unit. Mapping EQ-5D-5L to 3L. https://www.sheffield.ac.uk/nice-dsu/methods-development/mapping-eq-5d-5l-3l

Hernandez Alava, M., Pudney, S., Wailoo, A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. 2020; REPORT.

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Heitjan, F., Little, R. J. A. Multiple Imputation for the Fatal Accident Reporting System. Journal of the Royal Statistical Society. 1991; Series C 40:13–29.

Schenker, N., Taylor, J. M. G. Partially Parametric Techniques for Multiple Imputation. Computational Statistics and Data Analysis 1996;22:425–446.

Ratitch B, Lipkovich I, O'Kelly M. Combining analysis results from multiply imputed categorical data. PharmaSUG 2013; Paper SP03

12. Data Not Covered by This Plan

There are no plans for GBS department to analyze or summarize the following for the Clinical Study Report:

- Quantitative ECG measurements

[redacted]

[redacted]

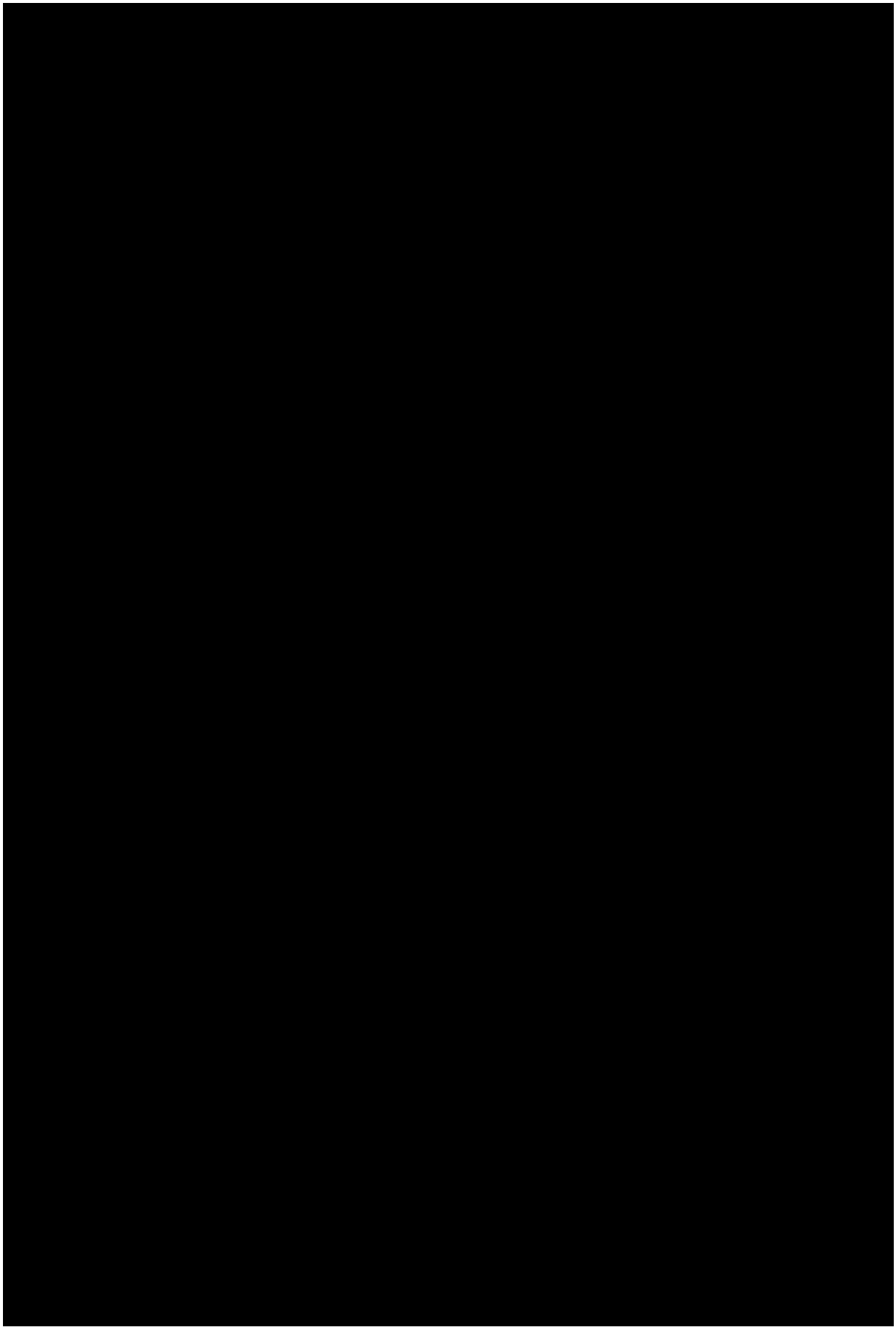
Above analyses will be conducted by Amgen Clinical Pharmacology Modeling and Simulation (CPMS).

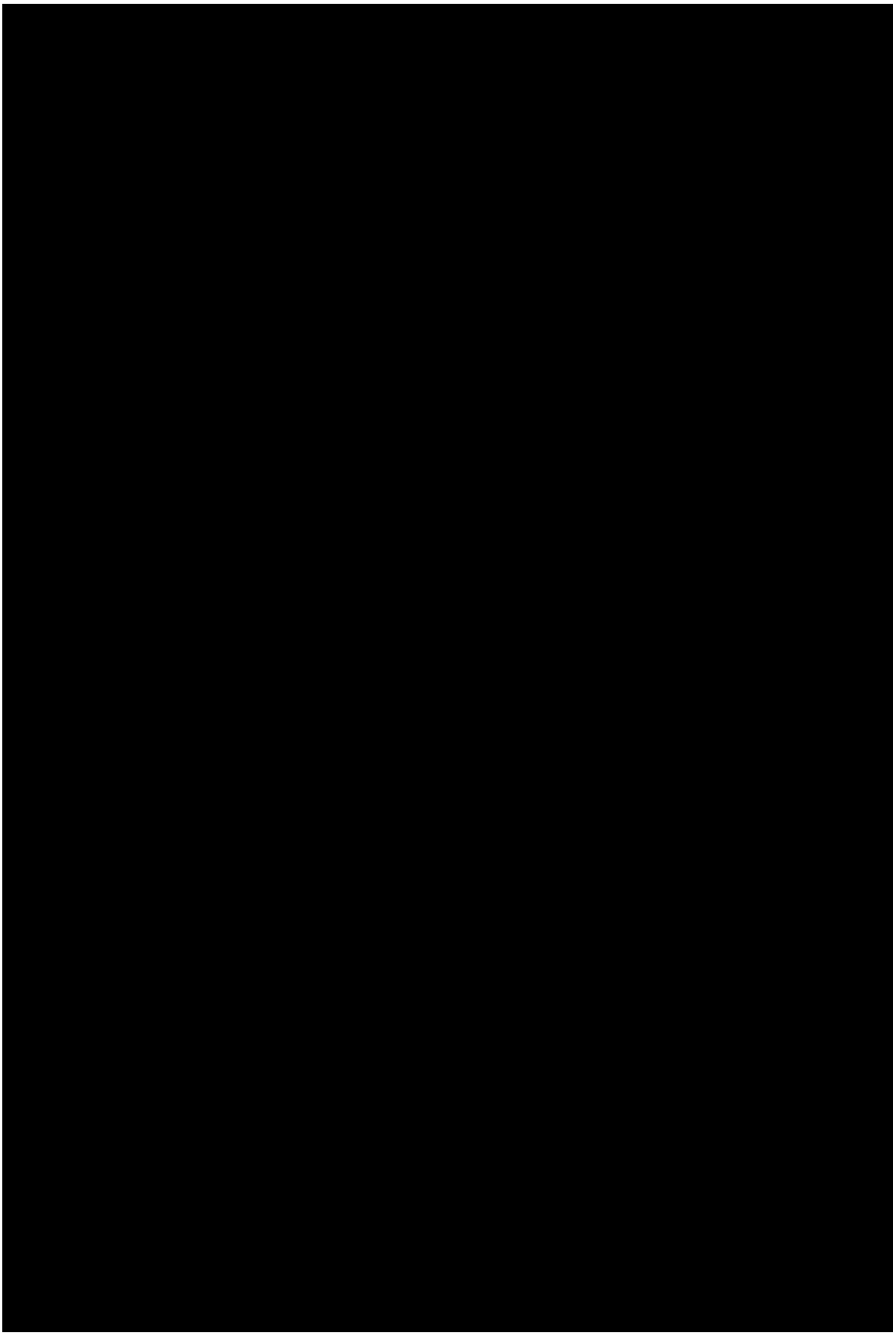
13. Appendices

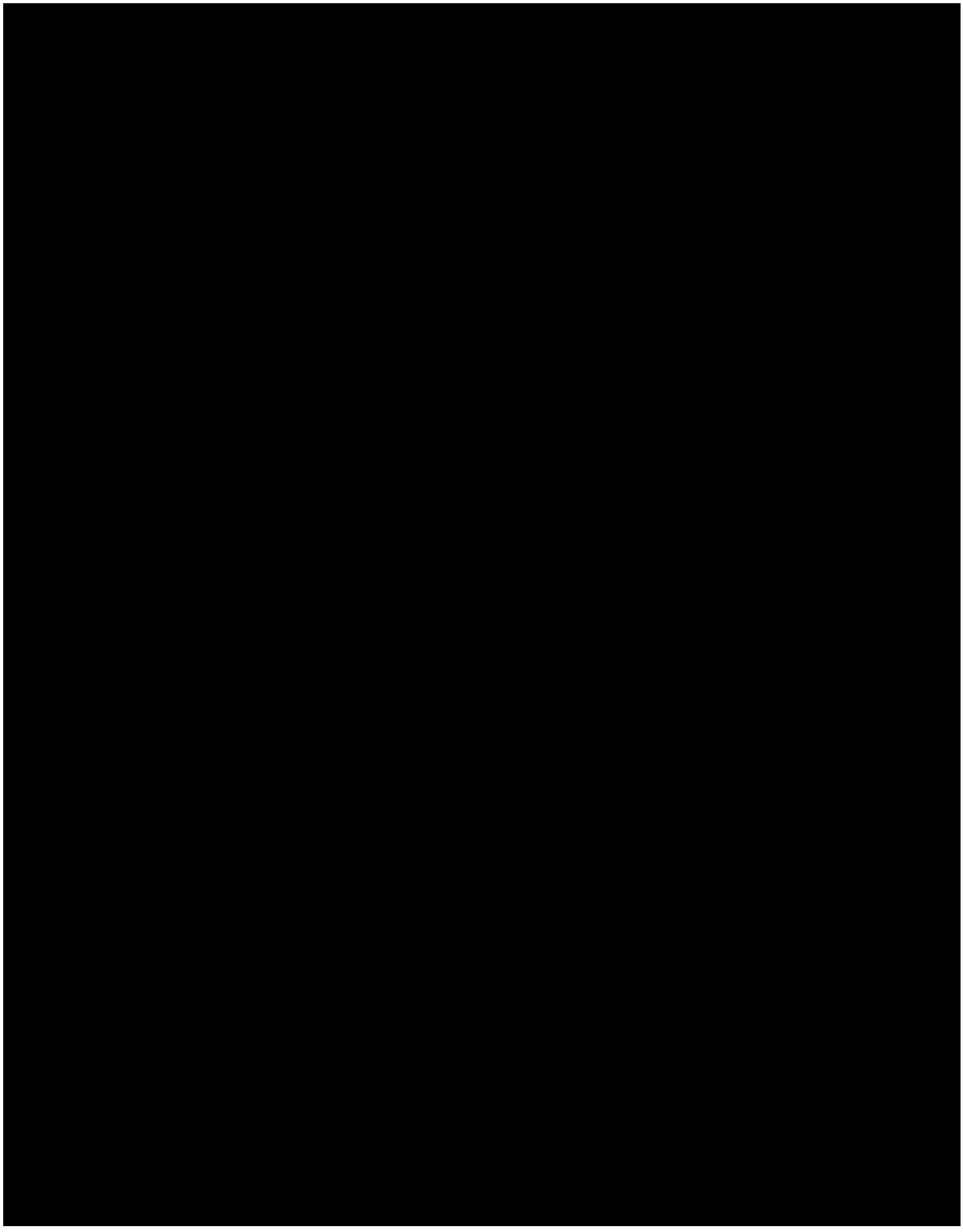
Appendix A. Reference Values/Toxicity Grades

Laboratory toxicity are graded based on NCI Common Toxicity Criteria version 5.0, which is available at the following:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf







Appendix C. Handling of Partial or Missing Start Dates of Adverse Events, Medications, and Procedures

Start Date	Imputation	Description
Missing Day	The first of the start month	Start date (yyyymm) ≠ first dose date (yyyymm) OR Start date (yyyymm) = first dose date (yyyymm) and stop date (yyyymmdd) < first dose date (yyyymmdd)
	First dose date	Start date (yyyymm) = first dose date (yyyymm) and stop date ≥ first dose date as determined based on one of the criteria in footnote [a]
Missing Day/Month	01JAN of the start year	Start date (yyyy) ≠ first dose date (yyyy) OR Start date (yyyy) = first dose date (yyyy) and stop date < first dose date as determined based on one of the criteria below: • Stop date (yyyymmdd) < first dose date (yyyymmdd); • Stop date (yyyymm) < first dose date (yyyymm) if day is missing in stop date
	First dose date	Start date (yyyy) = first dose date (yyyy) and stop date ≥ first dose date as determined based on one of the criteria in footnote [a]
Missing Day/Month/Year (Completely missing)	01JAN of the stop year	Stop date < the 1st dose date as determined based on one of the criteria below: • Stop date (yyyymmdd) < first dose date (yyyymmdd); • Stop date (yyyymm) < first dose date (yyyymm) if day is missing in stop date; • Stop date (yyyy) < first dose date (yyyy) if month and day are missing in stop date
	The 1st dose date	Stop date ≥ first dose date as determined based on one of the criteria in footnote [a]

[a]Criteria to determine stop date ≥ first dose date:

- Stop date is missing;
- Stop date (yyyymmdd) ≥ first dose date (yyyymmdd);
- Stop date (yyyymm) ≥ first dose date (yyyymm) if day is missing in stop date;
- Stop date (yyyy) ≥ first dose date (yyyy) if month and day are missing in stop date

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the month if day is missing or first day of the year if month is also missing.

Derivation Rules for Medication and Procedure Start Interval

Medication and procedure start interval will be set to 'RETREATMENT' if the imputed start date is after the first open-label retreatment dose date; else set to 'MAINTENANCE OR OPEN-LABEL' if the imputed start date is on or after the first maintenance or open-label treatment dose date ; else set to 'DOUBLE-BLIND' if the imputed start date is on or after the first dose date; else set to 'BEFORE' if the imputed start date is prior to the first dose date. For subjects who did not receive investigational product, the imputed start date will be compared with the enrollment date.

Derivation Rules for Medication and Procedure End Interval

Medication and procedure end interval will be set to 'RETREATMENT' if the end date is after the first open-label retreatment dose date; else set to 'MAINTENANCE OR OPEN-LABEL' if the imputed end date is on or after the first maintenance or open-label treatment dose date; else set to 'DOUBLE-BLIND' if the imputed end date is on or after the first dose date; else set to 'BEFORE' if the imputed end date is prior to the first dose date. If the medication and procedure end date is partial or missing, the medication and procedure end interval will be derived based on following rule:

End Date		**Interval for End Date**
Partial: yyyymm	< first dose date yyyymm	BEFORE
	≥ first dose date yyyymm	DOUBLE-BLIND
	≥ first maintenance/open-label treatment dose date yyyymm	MAINTENANCE OR OPEN-LABEL
	> first open-label retreatment dose date yyyymm	RETREATMENT

End Date		**Interval for End Date**
Partial: yyyy	< first dose date yyyy	BEFORE
	≥ first dose date yyyy	DOUBLE-BLIND
	≥ first maintenance/open-label treatment dose date yyyy	MAINTENANCE OR OPEN-LABEL
	> first open-label retreatment dose date yyyy	RETREATMENT
Completely missing		ONGOING

For subjects who did not receive investigational product, the end date will be compared with the randomization date.

Appendix D. Analytical Windows

The actual visit for a subject may not exactly coincide with their targeted visit date. Subjects who permanently discontinue investigational product and do not complete the remaining study visits through week 52 should complete the End of Treatment (EOT) visit at the next scheduled visit following last dose of investigational product. Complete efficacy and safety assessments will be collected at the EOT visit and be reported in the nominal week 52 visit in the database. All scheduled visits per protocol including EOT visits and unscheduled visits except for safety follow-up will be mapped to the analysis visits as in Table 13-1.

By-visit data collected at the safety follow-up visit do not belong to treatment period and will not be categorized into analysis visits. Any data occurred after EOS date will not be included in the analysis except antibody data.

Analysis Visit Window for Endpoints Based on Data Collection at Site Visits

Table 13-1 Analysis Visit Windows for Assessments Collected at Visits

Study Period	Visit	Target Day	Visit Window (Study Day)
Baseline	Baseline	1	See Baseline Assessment Definition in Section 5.3
Initiation Treatment Period	Week 2	15	2 to 22 for efficacy endpoints Or Day 1 post dose to 22 for safety related endpoints
	Week 4	29	23 to 43
	Week 8	57	44 to 71
	Week 12	85	72 to 99
	Week 16	113	100 to 127
	Week 20	141	128 to 155
	Week 24	169	156 to Week 24 visit day*, if available, else to 183
Open-label Treatment Period	Week 28 (Week 4 in OLT)	OLT Day 1 + 28	OLT Day 1 + 1 to OLT Day 1 + 42
	Week X+24 (Week X in OLT) X range: 8, 12,16, 20, 24	OLT Day 1+ X*7	OLT Day 1+ X*7-13 to OLT Day 1 + X*7+14
	Week 52 (Week 28 in OLT)	OLT Day 1 + 196	≥ OLT Day 1+ 183
Maintenance Treatment Period	Week 28 (Week 4 in MT)	MT Day 1 + 28	MT Day 1 + 1 to MT Day 1 + 42
	Week Y+24 (Week Y in MT) Y range: 8, 12,16, 20, 24	MT Day 1 + Y*7	MT Day 1 + Y*7-13 to min (MT Day 1 + Y*7+14, OLRT Day 1)

Study Period	Visit	Target Day	Visit Window (Study Day)
	Week 52 (Week 28 in MT)	MT Day 1 + 196	≥ MT Day 1+ 183, <= OLRT Day 1
Open-Label Retreatment Period	Week 4 in OLRT	OLRT Day 1+ 28	OLRT Day 1+ 1 to min (OLRT Day 1 + 42, Week 52 visit day)
	Week Z in OLRT Z range 8,12,16,20,24	OLRT Day 1+ Y*7	OLRT Day 1+ Y*7-13 to min (OLRT Day 1 + Y*7+14, Week 52 visit day)
Safety follow-up	Data collected on the safety follow-up visit will be summarized in safety follow-up visit without using analysis visit window above		

*Week 24 visit date is defined by the date vIGA-AD score is collected at nominal week 24. Week 52 visit date is defined by the date vIGA-AD score is collected at nominal week 52.

Note: If there are multiple sets of the same eCOA/PRO assessment done on the same day (eg, re-assessment is reported in web portal in addition to the original set reported in the eTablet), only one set of assessment per day for baseline and postbaseline will be selected for analysis based on the order described below:

1. Complete set will be chosen over the incomplete set (the complete status at the assessment level is defined as completing all expected questions of the assessment); for multiple incomplete sets on the same day, the one with most questions completed will be chosen.
2. The set with earliest timestamp will be chosen among remaining duplicates on the same day.

For postbaseline eCOA/PRO data, the selected assessment after step 2 will be considered as a scheduled visit if there is at least one set among the multiple sets of assessment with scheduled visit name. Otherwise, it will be considered as an unscheduled visit (ie, CPEVENT='UNSCHED').

Per protocol, all assessments will be collected prior to the dose at each visit except the vital signs collected during 2-hour post dose monitoring, which is for safety monitoring purpose and will not be included in analysis. For measurements taken on the same day as the IP administration, it will be assumed that these measurements are taken prior to the IP administration except for predose vital signs, labs, antibody and ECG on day 1, where the collection time of the assessment must be before the time of IP administration as defined in Section 5.3 Baseline Assessment.

For each assessment, if more than one visit with non-missing measurement (including the unscheduled visits, ie, CPEVENT = 'UNSCHED') fall within the same visit window during postbaseline, the following rules will be applied according to the order described below for selecting one visit per visit window for summary by visit:

1. There might be multiple scheduled visits and/or unscheduled visits in the same analysis visit window. The measurement for analysis in each analysis visit window will be selected according to the following order: EOT visit, the nominal scheduled visit corresponding to the analysis window, other scheduled visit and unscheduled visit(s).
2. If multiple unscheduled visits are mapped in the same analysis window without any scheduled visits, the unscheduled visit closest to the target day will be selected for analysis. If two unscheduled visits are equidistant from the target day, the latter visit will be selected for analysis.

Weekly Intervals for Efficacy Endpoints Derived From Daily Diary Collection

The weekly intervals derived from daily eDiary data collection will be utilized for following efficacy endpoints. Any eDiary data occurring after Week 52/EOT date will not be included in the analysis.

- Worst pruritus NRS
- AD skin pain NRS
- Sleep disturbance NRS

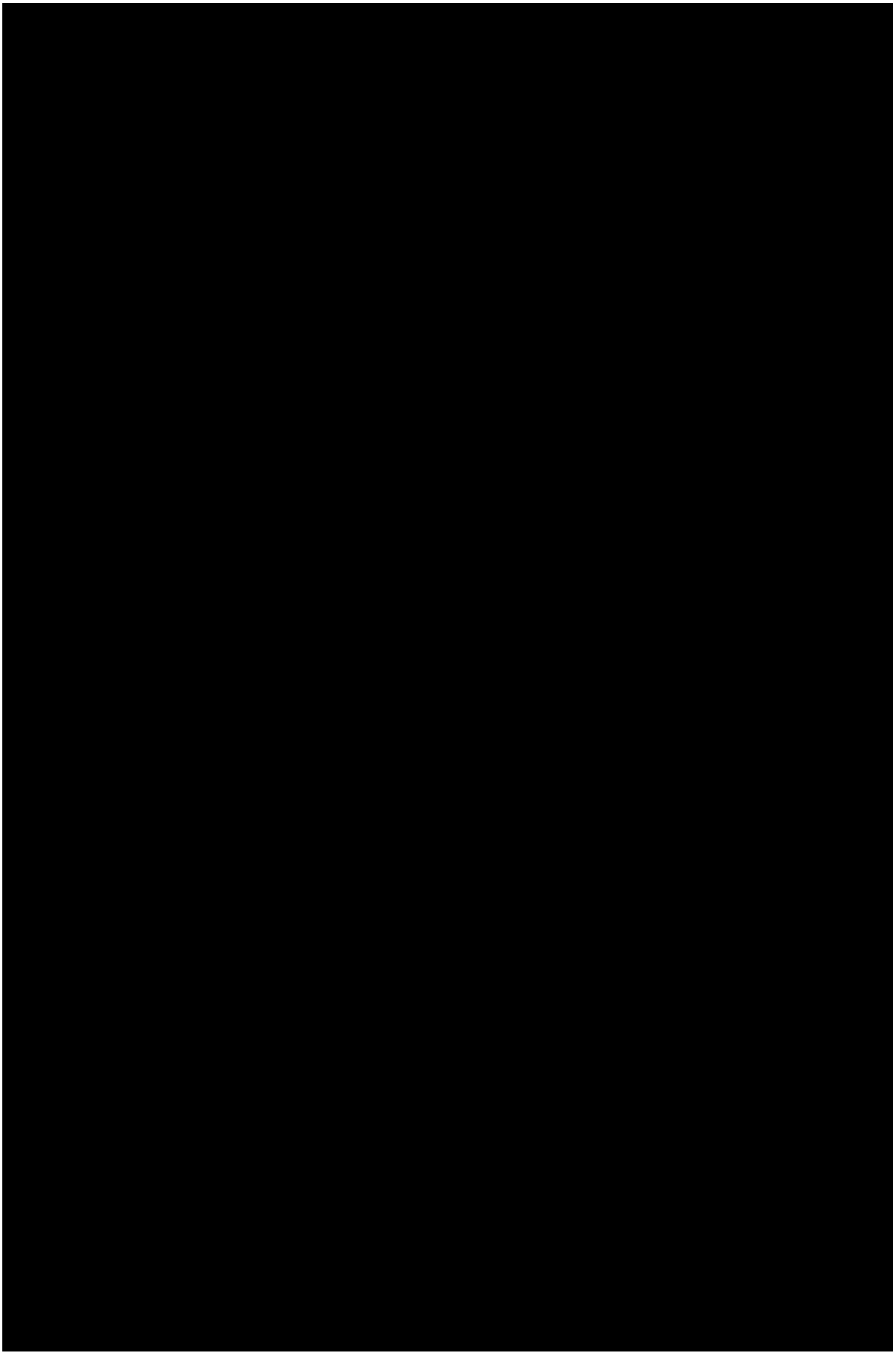
Table 13-2 Weekly Intervals for Efficacy Endpoints Derived From Daily eDiary Collection

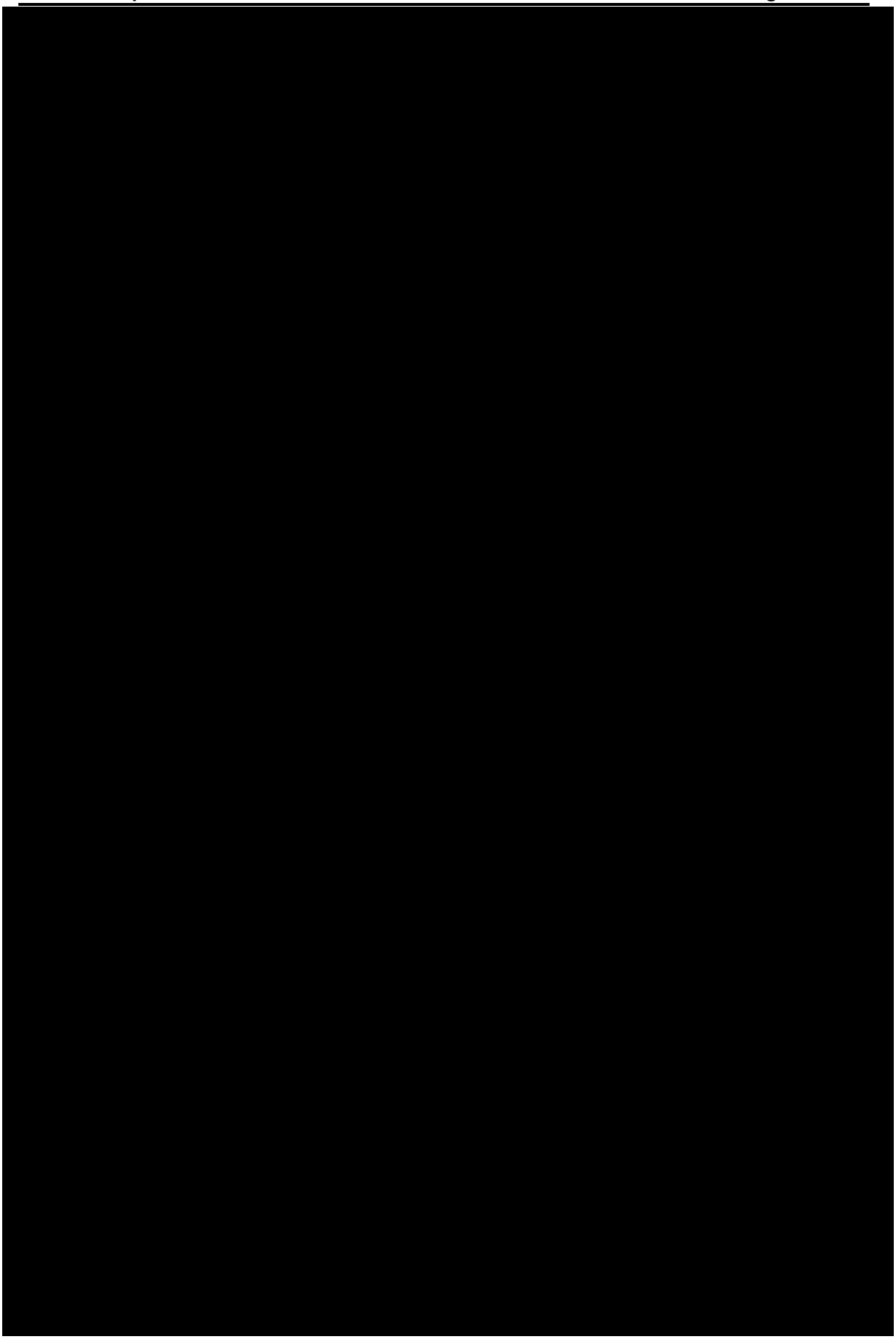
Study Period	Analysis Visit	Visit Window (Study Day)
Baseline	Baseline	7-day window including Day -6 to Day 1
Initiation Treatment period	Week 1	2 to 8
	Week 2	9 to 15
	Week 3	16 to 22
	Week 4	23 to 29
	Week 5	30 to 36
	Week 6	37 to 43
	Week 7	44 to 50
	Week 8	51 to 57
	Week 9	58 to 64
	Week 10	65 to 71
	Week 11	72 to 78
	Week 12	79 to 85
	Week 13	86 to 92
	Week 14	93 to 99
	Week 15	100 to 106

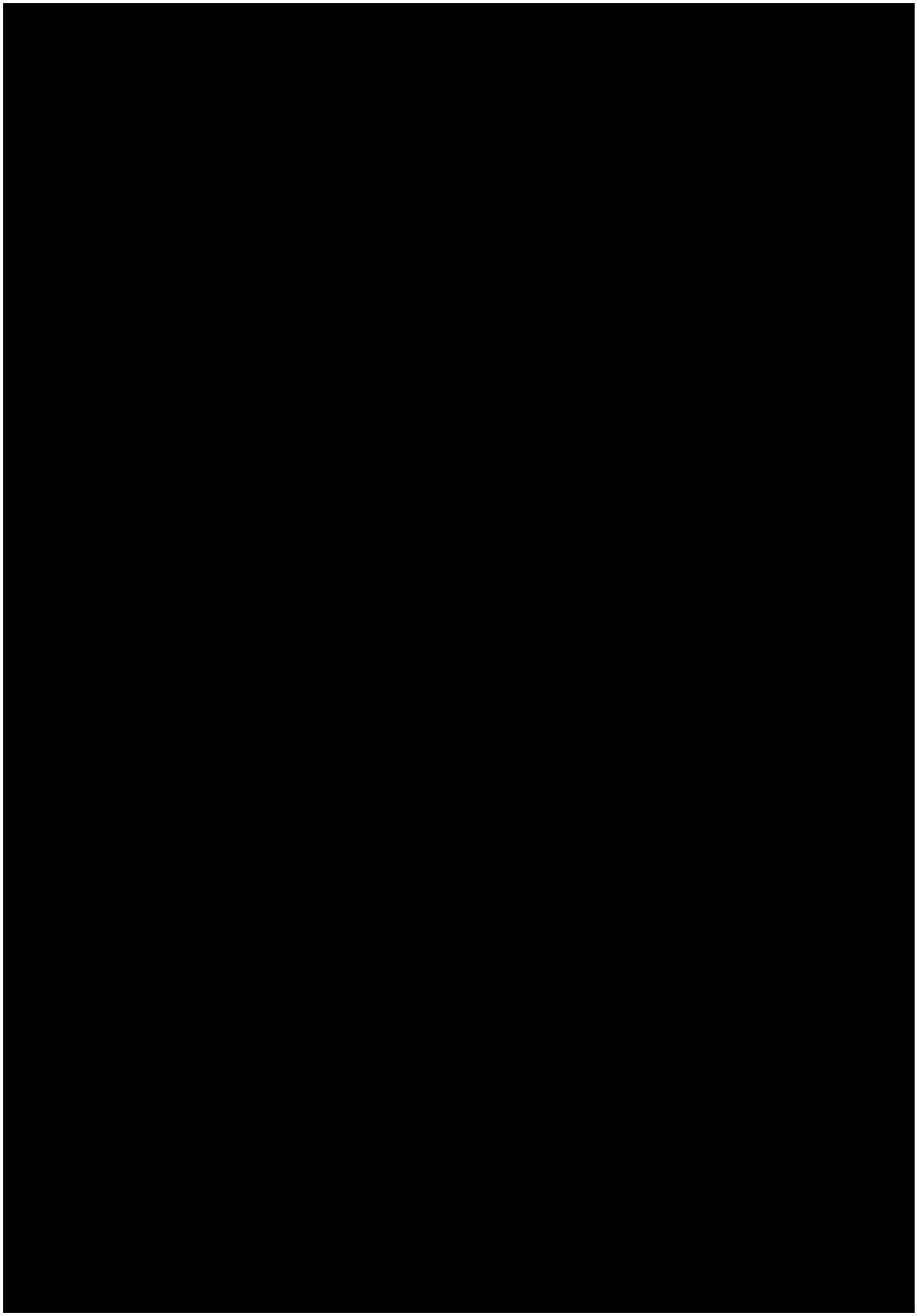
Study Period	Analysis Visit	Visit Window (Study Day)
	Week 16	107 to 113
	Week 17	114 to 120
	Week 18	121 to 127
	Week 19	128 to 134
	Week 20	135 to 141
	Week 21	142 to 148
	Week 22	149 to min (155, the day prior to WEEK 24 weekly visit window)
	Week 23	156 to min (162, the day prior to WEEK 24 weekly visit window)
	Week 24	7-day window ending on WEEK 24 visit day. Otherwise, 163 to 169 if no WEEK 24 visit. Note: The earliest WEEK 24 visit day is day 156 (See Table 13-1). The corresponding 7-day window can range from study day 150 to 156 inclusively. Therefore, the WEEK 22 and/or WEEK 23 weekly visit window(s) may need to be adjusted to avoid overlapping.
Open-label Treatment Period (OLT)	Week X+24 (Week X in OLT) Note: X range from 1 to 27	OLT Day 1 + X*7-6 to min (OLT Day 1 + X*7, the day prior to WEEK 52 weekly visit window)
	Week 52 (Week 28 in OLT)	7-day window ending on WEEK 52 visit day. Otherwise, OLT Day 1 +190 to OLT Day 1 +196 if no WEEK 52 visit.
Maintenance Treatment Period (MT)	Week Y+24 (Week Y in MT) Note: Y range from 1 to 27	MT Day 1 + Y*7-6 to min (MT Day 1 + Y*7, OLRT Day 1, the day prior to WEEK 52 weekly visit window)
	Week 52 (Week 28 in MT)	7-day window ending on WEEK 52 visit day. Otherwise, MT Day 1 +190 to MT Day 1 +196 if no WEEK 52 visit.
Open-label Retreatment Period (OLRT)	Week Z in OLRT Note: Z range from 1 to 28	OLRT Day 1 + Z*7-6 to Min (OLRT Day 1 + Z*7, Week 52 visit day)

Note: The date on which the daily assessment was reported will be used to determine the visit. The day prior to Day 1 is Day -1.

*Week 24 visit date is defined by the date week 24 vIGA-AD score is collected (AVISIT = Week 24 and ANL01FL = 'Y'). Week 52 visit date is defined by the date week 52 vIGA-AD score is collected (AVISIT = Week 52 and ANL01FL = 'Y').







Appendix G. Sample SAS Code for Efficacy Analysis