Statistical Analysis Plan

Protocol Title:	A Phase 3, Open-label, 52-week Study to Assess the Safety, Tolerability, and Efficacy of Rocatinlimab (AMG 451) in Adolescent Subjects Aged ≥ 12 to < 18 years With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit)
Short Protocol Title:	Phase 3 Study Assessing Rocatinlimab (AMG 451) in Adolescent Subjects With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit)
Protocol Number:	20210263
NCT Number:	NCT05633355
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SAP Date:	**Document Version** **Date** **Original (v1.0)** 31 March 2025

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	31 March 2025	

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List of Abbreviations

Abbreviation	Explanation
[redacted]	[redacted]
AD	atopic dermatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMQ	Amgen MedDRA Queries
AST	aspartate aminotransferase
BSA	body surface area
CRF	case report form
COVID-19	Coronavirus disease 2019
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
EASI 50	≥ 50% reduction from baseline in EASI score
EASI 75	≥ 75% reduction from baseline in EASI score
EASI 90	≥ 90% reduction from baseline in EASI score
EASI 100	100% reduction from baseline in EASI score
ECG	electrocardiogram
eCOA	electronic clinical outcome assessments
eCRF	electronic Case Report Form
[redacted]	[redacted]
EOI	event of interest
EOS	end of study
EOT	end of treatment
FAS	full analysis set
GBS	Global Biostatistical Science
HR	heart rate
IGA	Investigator's Global Assessment
IPD	important protocol deviation
JAK	janus kinase
MACE	major adverse cardiovascular events
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
PDE4	phosphodiesterase type 4
PK	pharmacokinetics

PRO	patient reported outcomes
Q4W	every 4 weeks
QTc	corrected QT interval
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
SBP	systolic blood pressure
SFU	safety follow-up
SMQ	Standardized MedDRA Queries
TBL	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
vIGA-AD™	Validated Investigator 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

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 4 for Study 20210263, Rocatinlimab (AMG 451) dated 17 September 2024. 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

Objectives	Endpoints
Primary	
• To describe the safety and tolerability of rocatinlimab in adolescents with moderate-to-severe AD	• Treatment emergent serious adverse events
Safety and Immunogenicity	
• To describe the safety and tolerability of rocatinlimab in adolescents with moderate to severe AD	• Treatment emergent adverse events (including clinically significant changes in laboratory values and vital signs)
[redacted]	

Exploratory	
• To describe the clinical response of rocatinlimab [redacted] mg treatment regimen 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 at assessment time points • Achieving a vIGA-AD score of 0 (clear) with ≥ 2-point reduction from baseline (vIGA-AD 0) response at assessment time points
• To describe the clinical response of rocatinlimab [redacted] mg treatment regimen at assessment time points, using vIGA-AD with an additional assessment of morphology	• Achieving vIGA-AD 1 response with presence of only barely perceptible erythema or vIGA-AD 0 response (revised Investigator's Global Assessment [rIGA™] 0/1) at assessment time points

• To describe the clinical response of rocatinlimab [redacted] mg treatment regimen using Eczema Area and Severity Index (EASI)	• Achieving ≥ 50% reduction from baseline in EASI score (EASI 50) at assessment time points • Achieving ≥ 75% reduction from baseline in EASI score (EASI 75) at assessment time points • Achieving ≥ 90% reduction from baseline in EASI score (EASI 90) at assessment time points • Achieving 100% reduction from baseline in EASI score (EASI 100) at assessment time points • Percent change from baseline in EASI score at assessment time points
[redacted]	

2.2 Hypotheses

This study is descriptive in nature, without a comparator arm. As such, no formal statistical hypothesis is defined.

3. Study Overview

3.1 Study Design

This is a phase 3, open-label, 52-week study to evaluate and provide supportive evidence of the safety, tolerability, and efficacy of rocatinlimab, in combination with topical therapy, in adolescent participants with moderate-to-severe AD with inadequate

response to topical medications. Approximately 170 adolescent participants will be enrolled in the study. Rocatinlimab will be administered subcutaneously at [redacted] mg Q4W for 52 weeks with one additional dose at week 2.

Use of topical corticosteroids (TCS) of high or super-high potency, topical phosphodiesterase type 4 (PDE4) inhibitors, topical janus kinase (JAK) inhibitors, phototherapy, or systemic therapies for AD during the 52-week study will be considered use of rescue therapy in the analysis.

A protocol defined [redacted] will apply to participants who do not demonstrate an adequate benefit after [redacted] weeks of treatment with the investigational product. Participants may continue investigational product treatment if any of the following criteria are met:

- At least 25% improvement in EASI from baseline
- At least 1 point improvement in Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD) from baseline

Participants who do not meet any of these criteria after [redacted] weeks of investigational product treatment will discontinue 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 investigational product. Participants who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and postdose monitoring procedures through week 52 for the evaluation of endpoints.

Participants may be eligible to enroll in the long-term maintenance Study [redacted] at week 52. A safety follow-up (SFU) visit is required [redacted] weeks after the last dose of investigational product for all participants who do not enroll into the long-term maintenance study [redacted]. An additional SFU visit will not be required for participants who discontinue investigational product but who complete the remaining study visits for at least [redacted] weeks after the last dose of investigational product before or at week 52.

3.2 Sample Size

Approximately 170 adolescent participants will be enrolled in the study. Assuming the dropout rate during the first 24 weeks being 10% and the subsequent 28 weeks being

20% of the remaining participants at week 24, it is expected that approximately 122 adolescent participants will be exposed to 52 weeks of rocatinlimab [redacted] mg.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Not applicable for primary safety endpoint.

4.2 Subgroups

Not applicable for primary safety endpoint.

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

5.1.1 Primary Endpoint

Treatment-emergent Serious Adverse Event (TESAE)

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

5.1.2 Safety Endpoints

Treatment-emergent Adverse Event (TEAE)

Events categorized as Adverse Events (AEs) starting after the first dose of investigational product, or 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-related TEAE

A treatment-related TEAE 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]

[redacted]

5.1.3 Exploratory 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 score 0 or 1 with ≥ 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

The Atopic Dermatitis Morphology Assessment (ADMA) is an additional assessment question of AD morphology completed for those participants with a vIGA-AD score of '1 – Almost clear': Barely perceptible erythema, no induration/papulation, no lichenification, and no oozing or crusting (Yes or No)?

The rIGA 0/1 response incorporates vIGA-AD 0/1 response and ADMA response, and is defined as achieving vIGA-AD 1 response with presence of only barely perceptible erythema (ie, ADMA response = Yes) or vIGA-AD 0 response and ≥ 2-point reduction from baseline.

Eczema Area and Severity Index (EASI)

The EASI evaluates the extent and severity of 4 key disease signs (Erythema, Edema/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.

Body Surface Area (BSA) Involvement of AD

The overall BSA affected by AD is estimated based on the palm area of the participant's hand. The surface area of the whole body is made up of approximately 100 palms or "handprints" (each entire palmar surface or "handprint" with closed fingers equates to approximately 1% of total body surface area). BSA affected AD is reported as a percentage ranging from 0% to 100% with higher score indicating more severe AD.

[redacted]

5.2 Study Dates

Informed Consent Date

The date on which participants signs the informed consent form.

Enrollment Date

Enrollment Date is defined as the date when participant was enrolled in the study.

First Investigational Product Dose Date

First investigational product dose date is the date on which a participant is administered the first dose of investigational product following enrollment, as recorded on the Investigational Product Administration eCRF. The first investigational product dose may be the same day or after the enrollment date.

Last Investigational Product Dose Date

Last investigational product dose date is the date on which a participant 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 participant is defined as the date when 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).

Participant-level End of Study (EOS) Date

End of study for each participant is defined as the date the participant 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 participant 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 participant across all sites has completed the assessments for EOS/SFU visit of the study.

5.3 Study Points of Reference

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, [redacted] 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 participants who are enrolled but not dosed after the enrollment, the baseline of the study is defined as the last nonmissing measurement prior to or on the date of enrollment.

Study Day 1

Study Day 1 is defined as the first investigational product dose date. For participants who are enrolled but not dosed after enrollment, the Study Day 1 is defined as the date of enrollment.

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.

Adverse Event Reporting Periods: First 24 Weeks, Post Week 24, and Overall

Adverse events during the entire study (overall) will also be summarized by the first 24 weeks and post week 24. Adverse events will be attributed to a treatment period of first 24 weeks versus post week 24 based on AE start date relative to date of study day 1 and week 24 doses, as follows:

First 24 weeks: Study Day 1 to MIN(week 24 dose date - 1, EOS date)

Post week 24: Week 24 dose date to EOS date

Any data occurred after EOS date will not be included in the analysis.

Note: For adverse events happening on the day of week 24 dose date, if the adverse event start time is before the IP administration time, then this adverse event should be included in the first 24 weeks.

5.4 Participant Disposition

Enrolled

Individuals are considered enrolled if they have been assigned to receive the investigational product. Enrolled individuals are referred to as “participants”.

On-study

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

Exposed to investigational product

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

Completing investigational product

Participants 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

Participants 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)

If participant received at least 1 dose of investigational product:

Exposure Duration (Days) = (minimum [last dose date + 27, end of study (EOS) date] - first dose date + 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 AD (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

Change From Baseline

Postbaseline 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.

Participant Incidence

The participant incidence for a given event is defined as the number of participants with at least one reported occurrence of the event divided by the number of participants (i.e., number of at-risk participants). Participants with multiple occurrences of the same event will only be counted once.

Time to Initiation of Rescue Therapy for AD During Treatment Period

Concomitant medications and phototherapies including rescue therapy for AD will be collected during the entire study period including safety follow-up. However, any use of rescue therapy for AD during safety follow-up after Week 52 visit will not impact the efficacy assessment.

For participants who received rescue therapy for AD during the 52-week treatment period, not including safety follow-up after Week 52 visit, time to event will be calculated as follows:

Time (days) = date of first use rescue therapy for AD – Study Day 1 date + 1

For participants who did not receive rescue therapy for AD during the 52-week treatment period, time to censorship will be at the end of the 52-week treatment period defined as follows:

Time (days) = Week 52 assessment date – Study Day 1 date + 1 for participants with last efficacy assessment in WEEK 52 analysis visit window (Appendix D, Table 13-1); or

Time (days) = earlier of (EOS Study Day, data cutoff – Study Day 1 date + 1 or Day 365 [target day of WEEK 52 analysis visit window]) for participants with last efficacy assessment before WEEK 52 analysis visit window.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set (FAS) includes all enrolled participants. Analyses of disposition, demographic and baseline data, Important Protocol Deviations (IPDs) or efficacy endpoints will utilize this analysis set.

6.2 Safety Analysis Set

The safety analysis set includes all participants who receive at least 1 dose of investigational product. Analyses of safety endpoints and summary of investigational product administration will utilize this analysis set.

TEAE will be summarized for the entire study and also by the first 24 weeks versus post week 24 separately, as defined in Section 5.3. Post week 24 summary will be generated based on participants who receive at least 1 dose of investigational product at week 24 or later.

[redacted]

7. Planned Analyses

7.1 Interim Analysis and Early [redacted]

Not Applicable.

7.2 Primary Analysis

The primary analysis will be conducted when all participants have completed the week 52/EOT visit, and the data have been entered, cleaned, and locked. The objective of the primary analysis is to describe safety and [redacted] on all participants over the 52-week treatment period and additional safety data available only for participants who do not enroll in the long-term maintenance study.

7.3 Final Analysis

The final analysis will be conducted at the end of the study when all participants have entered the extension study or completed the EOS visit, and the data have been entered, cleaned, and locked. The objective of the final analysis is to describe complete safety data through EOS on all participants 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, [redacted] 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 [redacted] 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.

[redacted]

[redacted]

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

8.4 Detection of Bias

Factors that may bias the results of the study include:

- important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- 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.

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

The term “Subject” and “Participant” will be used synonymously in datasets, tables, figures, and listings.

Participant disposition, demographics, and baseline disease characteristics will be summarized descriptively. 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.

9.2 Participant Accountability

The number and percent of participants who were enrolled, received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing, completed study, discontinued study and reasons for discontinuing will be summarized. Summary of participants who discontinue investigational product/study due to COVID-19 control measures may be included.

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

The number and percent of participants enrolled 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 participant’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 participants 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 on FAS. If multiple races have been reported for a participant, the participant will be categorized as multiple race.

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)
- Severity of disease
- Geographical region
- Medical history
- Prior treatment for AD with reason for [redacted]
- Selected clinical outcome assessment (COA) at baseline

9.5 Efficacy Analyses

CCI

[redacted]

9.5.1 Primary Estimands

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. Participants are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and postdose monitoring procedures through week 52 after permanent discontinuation of investigational product for evaluation of endpoints.

The following primary estimands will be implemented to handle intercurrent events specifically according to the [redacted] clinical questions of interest.

The primary estimand for a binary endpoint (Section 2.1) is to measure the effect of rocatinlimab as assessed by the response rate in rocatinlimab [redacted] mg among enrolled participants within moderate-to-severe AD adolescent population in the situation that rescue therapy use for AD or permanent discontinuation of investigational product due to protocol specified criteria did not occur. Participants initiating rescue therapy for AD or permanently discontinuing investigational product due to protocol-specified criteria for lack of efficacy (Section 3.1) will be classified as nonresponders at all subsequent time points (composite strategy reflecting lack of response). For participants who do not use rescue therapy for AD, but permanently discontinue investigational product due to other reasons, 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 means of change or percent change from baseline value in rocatinlimab [redacted]mg among enrolled participants within moderate-to-severe AD adolescent population in the situation that rescue therapy use for AD or permanent discontinuation of investigational product due to protocol specified criteria did not occur. Participants initiating rescue therapy for AD or permanently discontinuing investigational product due to the protocol-specified criteria for lack of efficacy (Section 3.1) will be included in the analysis, and each participant's worst observation, including baseline value, before initiation of rescue therapy for AD or permanently discontinuing investigational product due to the protocol-specified criteria for lack of efficacy will be carried forward (WOCF) to all subsequent time points (composite strategy reflecting lack of response). For participants who do not use rescue therapy for AD but permanently discontinue investigational product due to other reasons, 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 those intercurrent events.

Table 9-1. Primary Estimands

Endpoint Type	Intercurrent Events		
	Rescue Therapy Initiation for AD	Permanent Investigational Product Discontinuation	
		Due to Protocol-specified Criteria for Lack of Efficacy	Due to Other Reasons
Binary	Composite strategy: • Set to Nonresponder	Composite strategy: • Set to Nonresponder	Treatment policy strategy: Keep observed data
Continuous	Composite strategy: • WOCF	Composite strategy: • WOCF	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).

9.5.2 Missing Data Imputation Methods

Remaining missing data after applying the strategy for each intercurrent event will be imputed using multiple imputation (MI) under missing at random (MAR) assumption.

MI by fully conditional specification (FCS-MI) will be used to impute missing data of monotone or non-monotone pattern. For continuous efficacy measurements, the regression and predictive mean matching (REGPMM) method available in the FCS statement of SAS PROC MI is used to impute missing values. Rounding on the imputed values is not needed as REGPMM method imputes a value randomly from a set of observed values whose predicted values are closest to the predicted value for the missing value from the simulated regression model (Heitjan and Little, 1991; Schenker and Taylor, 1996). Multiply imputed efficacy measurements (eg, vIGA-AD score, EASI total score) will be further derived to the corresponding binary or continuous endpoint(s) for analysis (eg, vIGA-AD 0/1, percent change from baseline in EASI score, EASI 75 or EASI 90) before being analyzed with the specified analysis method. To ensure consistency between multiply imputed efficacy measurements and the corresponding binary response endpoints with respect to the implementation of composite strategy reflecting lack of response, WOCF will be applied to continuous efficacy measurements before conducting multiple imputation on remaining missing data. Analysis results following the analysis method (Section 9.5) from each imputed complete data set will be combined into a single inferential result using SAS PROC MIANALYZE based on Rubin's rules.

Under missing at random (MAR) assumption, corresponding efficacy measurements at each postbaseline timepoint will be imputed with relevant baseline and postbaseline data and the severity of disease included in the imputation model.

For each MI process, 100 sets of complete data will be imputed if there is no efficiency issue. See detailed implementation in Appendix F.

The initial seeds used in each MI process are listed in table below.

Table 9-2. Seed Values Used in Multiple Imputation

Efficacy Measurement	Seed Values for MI
vIGA-AD score[a]	62496735
EASI total score	99426283
BSA	88820620

[a] The vIGA-AD score and the corresponding AD morphologic assessment response when vIGA-AD score = 1 will be incorporated when performing multiple imputation such

that the imputed data can be used to derive both vIGA-AD 0/1 response and rIGA 0/1 response to ensure consistency.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

The safety analysis set will include all enrolled participants who received at least 1 dose of investigational product during the study. Participant incidence of treatment emergent adverse events and serious adverse events will be summarized using descriptive statistics including but not limited to frequency and percentages.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

Participant incidence of all TEAE, TESAE, TEAE leading to discontinuation of investigational product, treatment-related TEAE, and fatal TEAE will be tabulated by system organ class and by preferred term in descending order of frequency. Selected TEAE and TESAE summary tables will be tabulated by preferred term in descending order of frequency.

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

Adverse event of interest (EOI: Appendix E) will include but not 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, hemorrhage, or perforation.

Participant incidence of EOI (standardized MedDRA queries and/or Amgen Medical Queries) will also be summarized according to their categories and preferred term

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.
- 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, as applicable

- Summary of grades ≥ 3 laboratory toxicities for selected laboratory parameters, as applicable
- Participant 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 (> 1.5x ULN)

9.6.4 Vital Signs

The analyses of vital signs will include summary statistics over time. Participant incidence of the following defined categories for systolic/diastolic 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 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]

[redacted]

9.6.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product.

9.6.9 Exposure to Concomitant Medication

Number and percentage of participants receiving rescue therapy for AD will be summarized by medication of interest category. In addition, number and percentage of participants receiving TCS of low/medium potency will also be summarized. See Appendix B for a list of selected medications and their groupings.

[redacted]

[redacted]

10. Changes From Protocol-specified Analyses

There are no changes from the protocol-specified analyses.

11. Literature Citations / References

CCI [redacted]

[redacted]

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]

CCI [redacted]

13. Appendices

Appendix A. Reference Values/Toxicity Grades

Laboratory toxicities 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 B. Atopic Dermatitis Medication of Interest Category and Definition

Prior and on-study atopic dermatitis therapies will be summarized based on the following categories and definitions. Rescue therapies include a subset of on-study therapies used specifically for atopic dermatitis, as indicated as for "ATOPIC DERMATITIS AND RELATED CONDITIONS" on the Concomitant Medication eCRF or Procedure eCRF (for phototherapies only). Additional preferred terms for newly approved therapies may be added without an amendment to the SAP.

Medication of Interest (MOI) Category	Definition
Topical Therapies	
Topical calcineurin inhibitors (TCI)	Includes the following preferred terms with route = TOPICAL • PIMECROLIMUS • TACROLIMUS • TACROLIMUS MONOHYDRATE Note: TCI is not considered as rescue therapy in this study.
Topical corticosteroids (TCS)	Includes ATC code = D07 (CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS) with route = TOPICAL Includes the following TCS combination therapies under ATC code = D05 (ANTIPSORIATICS) with route = TOPICAL: • BETAMETHASONE BUTYRATE PROPIONATE; MAXACALCITOL • BETAMETHASONE DIPROPIONATE; CALCIPOTRIOL • BETAMETHASONE DIPROPIONATE; CALCIPOTRIOL MONOHYDRATE Includes additional TCS combination therapies under ATC code = D01 (ANTIFUNGALS FOR DERMATOLOGICAL USE) with route = TOPICAL and containing the following TCS components: • BETAMETHASONE DIPROPIONATE • CLOBETASOL PROPIONATE • DIFLUCORTOLONE VALERATE • FLUPREDNIDENE ACETATE • HYDROCORTISONE • TRIAMCINOLONE

Medication of Interest (MOI) Category	Definition
	• TRIAMCINOLONE ACETONIDE Note: Formulation and strength are also collected for each TCS record on the eCRF. The potency level (low/medium, high/super-high, or unknown) of each TCS is determined following the reference Table 11-4 Topical Corticosteroids Potency Category in the Protocol Appendix 8 and blinded medical review. Only TCS of high/super-high or unknown potency is considered as rescue therapy in this study.
Topical PDE4 inhibitors	Includes the following preferred terms • CRISABOROLE • DIFAMILAST • ROFLUMILAST with route = TOPICAL
Topical JAK inhibitors	Includes the following preferred terms • DELGOCITINIB • IVARMACITINIB with route = TOPICAL • RUXOLITINIB; RUXOLITINIB PHOSPHATE • TOFACITINIB; TOFACITINIB CITRATE with route = TOPICAL
Other topical therapy	Includes the following preferred term • TAPINAROF
Emollients	Includes ATC code = D02 (EMOLLIENTS AND PROTECTIVES) or preferred terms of HEPARIN or HEPARIN SODIUM with route = TOPICAL Note: Emollient is not considered as rescue therapy.
Systemic Therapies	
Phototherapies	Includes the following procedure codes: • UVA Therapy • PUVA Therapy • Broadband UVB phototherapy • Narrowband UVB phototherapy
Systemic PDE4 inhibitors	Preferred term = APREMILAST
Systemic corticosteroids	Includes ATC code = H02 (CORTICOSTEROIDS FOR SYSTEMIC USE) with the following systemic routes: • INTRAMUSCULAR • INTRAPERITONEAL • INTRATHECAL • INTRAVENOUS • NASOGASTRIC • ORAL • SUBCUTANEOUS
Conventional Immunosuppressants	• Route = ORAL and preferred term = CICLOSPORIN

Medication of Interest (MOI) Category	Definition

	• Route = INTRAMUSCULAR, ORAL, or SUBCUTANEOUS with the following preferred terms:
	  ○ METHOTREXATE
	  ○ METHOTREXATE SODIUM
	• Route = ORAL and preferred term = AZATHIOPRINE
	• Route = ORAL with the following preferred terms:
	  ○ MYCOPHENOLATE MOFETIL
	  ○ MYCOPHENOLATE SODIUM
	  ○ MYCOPHENOLIC ACID
	• Route = ORAL or SUBCUTANEOUS and preferred term = TACROLIMUS

Biologics	Includes the following preferred terms: • ADALIMUMAB • BENRALIZUMAB • BRODALUMAB • CENDAKIMAB • DUPILUMAB • EBLASAKIMAB • ETOKIMAB • INFLIXIMAB • LEBRIKIZUMAB • NEMOLIZUMAB • OMALIZUMAB • RITUXIMAB • TELAZORLIMAB • TEZEPELUMAB • TRALOKINUMAB; TRALOKINUMAB LDRM • USTEKINUMAB
Systemic JAK inhibitors	Includes the following preferred terms • ABROCITINIB • BARICITINIB • IVARMACITINIB with route = ORAL • TOFACITINIB; TOFACITINIB CITRATE with route = ORAL • UPADACITINIB; UPADACITINIB HEMIHYDRATE

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 < 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; • Stop date (yyyy) < first dose date (yyyy) if month and day are missing in stop date
	First 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 participants 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 'BEFORE' if the end date is prior to the first dose date; else 'OPEN-LABEL'. For participants 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 'BEFORE' if the end date is prior to the first dose date; else 'OPEN-LABEL'. 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	OPEN-LABEL
Partial: yyyy	< first dose date yyyy	BEFORE
	≥ first dose date yyyy	OPEN-LABEL
Completely missing		ONGOING

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

Appendix D. Analytical Windows

The actual visit for a participant may not exactly coincide with their targeted visit date. Participants 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.

Table 13-1. Analysis Visit Window for Endpoints Based on Data Collection at Site Visits

Analysis Visit	Target Day	Visit Window (Study Day)
BASELINE	1	See Baseline Assessment definition in Section 5.3
WEEK 2	15	2 to 22
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 183
WEEK 28	197	184 to 211
WEEK 32	225	212 to 239
WEEK 36	253	240 to 267
WEEK 40	281	268 to 295
WEEK 44	309	296 to 323
WEEK 48	337	324 to 351
WEEK 52	365	≥ 352
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	

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 postdose monitoring, which is for safety monitoring purpose and will not be included in the analysis. For measurements taken on the same day as the investigational product administration, it will be assumed that these measurements are taken prior to the investigational product 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 investigational product administration as defined in Section 5.3 Baseline Assessment.

For each assessment, if more than one visit with nonmissing 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.

Appendix E. Event of Interest (EOI)

Events of interest are defined based on standardized MedDRA queries (SMQ), Amgen Medical Queries (AMQ), or event classification codes and subcodes (presented in parentheses and brackets, respectively) for positively adjudicated serious cardiovascular events as follows:

Major Category	Sub-category	Search Strategy or Definition
Injection-related Reactions (IRR)	N/A	• Injection-related reaction AMQ within 72 hours of injection (Narrow)
Hypersensitivity	N/A	• Hypersensitivity AMQ (Narrow)
Anaphylactic reactions	N/A	• Anaphylactic reaction SMQ (Narrow)
Injection site reactions	N/A	• Injection site reactions AMQ (Narrow)
Infections	All infections	• Infections and infestations SOC
	Serious infections	• Infections and infestations SOC and serious = Yes
	Tuberculosis	• Tuberculosis AMQ (Broad)
	Opportunistic infections	• Opportunistic infections SMQ (Narrow)
	Infections requiring systemic antibiotic therapy	• Infections and infestations SOC and action taken = Systemic antibiotic therapy
	COVID-19	• COVID-19 SMQ (Narrow)
Malignancy	N/A	• Malignant or unspecified tumors SMQ (Narrow)
[redacted]	[redacted]	• [redacted]
		• [redacted]
		• [redacted]
Conjunctivitis	N/A	• Conjunctivitis AMQ (Narrow)
Aphthous ulcer	N/A	• Stomatitis and ulceration AMQ (Narrow)
Gastrointestinal ulceration, hemorrhage, or perforation	N/A	• Gastrointestinal perforation, ulceration, haemorrhage or obstruction SMQ (narrow)
Cardiovascular events	MACE	CCI [redacted]

Major Category	Sub-category	Search Strategy or Definition
		CCI
	Extended MACE	CCI
	Other cardiovascular events	

Major Category	Sub-category	Search Strategy or Definition
		CCI
	All positively adjudicated serious cardiovascular events	

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

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Note: When performing multiple imputation for binary endpoints (eg, vIGA-AD 0/1, EASI 75), if there are no missing values or only a small number of missing values in the

original dataset (eg, vIGA-AD response, total EASI score), 100 sets of derived binary endpoints of interest will likely be identical. This will then yield 100 sets of identical estimates resulting in zero between-imputation variance in Rubin's rule. In this scenario, the combined multiple imputation result is equivalent to single-dataset analysis, and only the first imputed dataset will be analyzed to report the combined multiple imputation result without using PROC MIANALYZE. This special handling is to avoid SAS warning messages when calling PROC MIANALYZE with identical estimates from the multiple imputed datasets.

Product: Rocatinlimab (AMG 451)	**Protocol Number:** 20210263
Database Snapshot Date: [redacted]	
SAP/OR-SAP/SSAP Author: [redacted]	**FORM completion Date:** **23 June 2025**

Changes to Planned Analyses:

This FORM provides revisions for the SAP original version approved on 31 March 2025.

Effective

1) Pubertal maturation self-assessment (Tanner Staging) was implemented in protocol amendment 1. However, the corresponding analysis was inadvertently omitted in Section 9.6 Safety Analyses of the Statistical Analysis Plan.

   The self-assessment of Tanner Staging for pubertal maturation at baseline and postbaseline visits will be summarized by gender.

2) Appendix D. Analytical Windows

   - Define WEEK 2 analysis visit window separately for efficacy endpoints and safety related endpoints
   - [redacted]

Previous:

Analysis Visit	Target Day	Visit Window (Study Day)
WEEK 2	15	2 to 22

Revised:

Analysis Visit	Target Day	Visit Window (Study Day)
WEEK 2	15	2 to 22 **for efficacy endpoints or Day 1 postdose to Day 22 for safety related endpoints (excluding nominal visits D3 and D7 for vital sign)**
DAY 3*	**Nominal Visit D3**	

DAY 7*	**Nominal Visit D7**

***The visit windows for DAY 3 and DAY 7 are defined as the nominal visit D3 and D7, respectively, which is differentiated from other analysis visits.**

[redacted]

4) Correct a typo in Appendix C Handling of Partial or Missing Start Dates of Adverse Events, Medications, and Procedures

   Previous:
   Medication and procedure start interval will be set to 'BEFORE' if the end date is prior to the first dose date; else 'OPEN-LABEL'.

   Revised:
   Medication and procedure start interval will be set to 'BEFORE' if the **imputed start** date is prior to the first dose date; else 'OPEN-LABEL'.

Effective

Approved by GSL: [redacted]

Approved by study lead (*indicate applicable role such as: EDL/GDL/GMAL/CfOR/HEOR*): [redacted]