Statistical Analysis Plan

Protocol Title:	A Phase 3, 24-week, Randomized, Placebo-controlled, Double-blind Study to Assess the Effect of Rocatinlimab on Vaccine Antibody Response in Adult Subjects With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET – VOYAGER)
Short Protocol Title:	A Phase 3 Study Assessing Rocatinlimab on Vaccine Antibody Response in Moderate-to-severe AD (ROCKET – VOYAGER)
Protocol Number:	20210158
NCT Number:	NCT05899816
Authors:	[redacted]
Sponsor:	Amgen, Inc. One Amgen Center Drive Thousand Oaks, CA, 91320
SAP Date:	**Document Version** **Date** **Original (v1.0)** 01 November 2024

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	01NOV2024	

Table of Contents

List of Tables

List of Figures

No table of figures entries found.

List of Abbreviations

Abbreviation	Explanation
AD	atopic dermatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMR	analytical measuring range
AST	aspartate aminotransferase
CI	confidence interval
[redacted]	
COA	clinical outcome assessment
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	case report form
CTCAE	common terminology criteria for adverse events
DBP	diastolic blood pressure
EASI	Eczema Area and Severity Index
EASI 75	achievement of ≥ 75% reduction from baseline in EASI score
ECG	electrocardiogram
eCOA	electronic clinical outcome assessments
eCRF	electronic case report form
[redacted]	
EOI	event of interest
EOS	end of study
EOT	end of treatment
FAS	full analysis set
GBS	Global Biostatistical Science
HADS	Hospital Anxiety and Depression Scale
HR	heart rate
IGA	Investigator's Global Assessment
IgG	immunoglobulin G
IPD	important protocol deviation
IRAS	Immune response analysis set
JAK	janus kinase
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
PDE4	phosphodiesterase type 4

Abbreviation	Explanation
PRO	patient-reported outcome
[redacted]	
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
SSAP	supplement statistical analysis plan
TBL	total bilirubin
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
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

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 1 for study 20210158, Rocatinlimab (AMG 451) dated 30 June 2023. 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.

The analysis plan for the wearable device substudy will be provided in separate Supplement Statistical Analysis Plan (SSAP).

2. Objectives, Endpoints/Estimands and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To estimate vaccine response in rocatinlimab group vs placebo group, assessed using antibody antitetanus response at week 24	• Positive antitetanus response at week 24 defined as the antibody response to tetanus vaccine assessed by measuring serum antitetanus immunoglobulin G (IgG) by an immunoassay
• To estimate vaccine response in rocatinlimab group vs placebo group, assessed using antibody antimeningococcal response at week 24	• Positive antimeningococcal response at week 24 defined as the antibody response to meningococcal vaccine assessed by measuring serum antimeningococcal IgG by an immunoassay
Safety and Immunogenicity	
[redacted]	
Exploratory Efficacy	
[redacted]	

Objectives	Endpoints
[redacted]	

Primary Estimands for Exploratory Efficacy Endpoints

Two intercurrent events will be considered to estimate the rocatinlimab treatment effects based on exploratory efficacy endpoints: initiation of rescue therapy for AD (Appendix B) and permanent discontinuation of investigational product without rescue therapy for AD. Subjects are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and postdose monitoring procedures through week 24 after permanent discontinuation of investigational product for evaluation of endpoints.

The primary estimand for a binary exploratory efficacy endpoint is to measure the effect of rocatinlimab as assessed by the difference in response rates between rocatinlimab [redacted] 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 (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).

All exploratory efficacy endpoints are binary endpoints in this SAP. Hence, estimand for a continuous endpoint is not appliable.

2.2 Hypotheses

No formal statistical hypothesis will be tested in this study, and all analyses will be descriptive.

3. Study Overview

3.1 Study Design

This is a phase 3, randomized, 24-week, double-blind study to evaluate the efficacy of antitetanus and antimeningococcal vaccination in rocatinlimab-treated adult subjects with moderate-to-severe AD.

Approximately [redacted] eligible subjects will be randomized in a [redacted] ratio to 2 treatment groups for a duration of 24 weeks as follows:

- Rocatinlimab [redacted] mg [redacted] with loading dose at week [redacted] (N = [redacted]
- Placebo [redacted] with a loading dose at week [redacted] (N = [redacted]

Randomization will be stratified by baseline disease severity (moderate Validated Investigator's Global Assessment for Atopic Dermatitis [vIGA-AD score = 3] versus severe [vIGA-AD score = 4]). Tetanus and meningococcal vaccines will both be administered at the week [redacted] visit for each subject.

Except for topical corticosteroids (TCS) of low/medium potency, the use of other topical or systemic therapies for AD during the 24-week treatment period will be considered use of rescue therapy for assessing exploratory efficacy endpoints. Refer to Appendix B for more details.

Subjects who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures, including the vaccine administrations at week [redacted] and the vaccine IgG antibody samples at week [redacted] and week 24, with the exception of investigational product administration and post-dose monitoring procedures through week 24 for the evaluation of the primary endpoints.

Subjects may be eligible to enroll in the long-term maintenance Study [redacted] at week 24. 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 long-term maintenance study. An additional SFU visit will not be required for subjects 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 24.

3.2 Sample Size

[redacted]

	Active (%)	Placebo (%)	Vaccine Response Rate Difference (%) (Active – Placebo) (95% CI)	Halfwidth of 95% CI
Antitetanus				
Tralokinumab (N = 87:76)	92	96.1	-4.1 (-11.3, 3.1)	7.2
Dupilumab (N = 90:92)	83.3	83.7	-0.4 (-11, 10)	11
Antimeningococcal				
Tralokinumab (N = 87:76)	86	84.2	1.8 (-9.2, 12.8)	11
Dupilumab (N = 90:92)	86.7	87	-0.3 (-10, 10)	10
Study 20210158 (N = 130:65)	80	80	0 (-12, 12)	12
	85	85	0 (-11, 11)	11
	90	90	0 (-9, 9)	9

A sample size of [redacted] is planned. Assuming [redacted] respectively, please see above table for reference.

4. Covariates and Subgroups

4.1 Planned Covariates

Analyses of primary and exploratory efficacy (binary) endpoints will be adjusted for the effect of the stratification factor baseline disease severity (moderate [vIGA-AD score = 3] versus severe [vIGA-AD score = 4]).

4.2 Subgroups

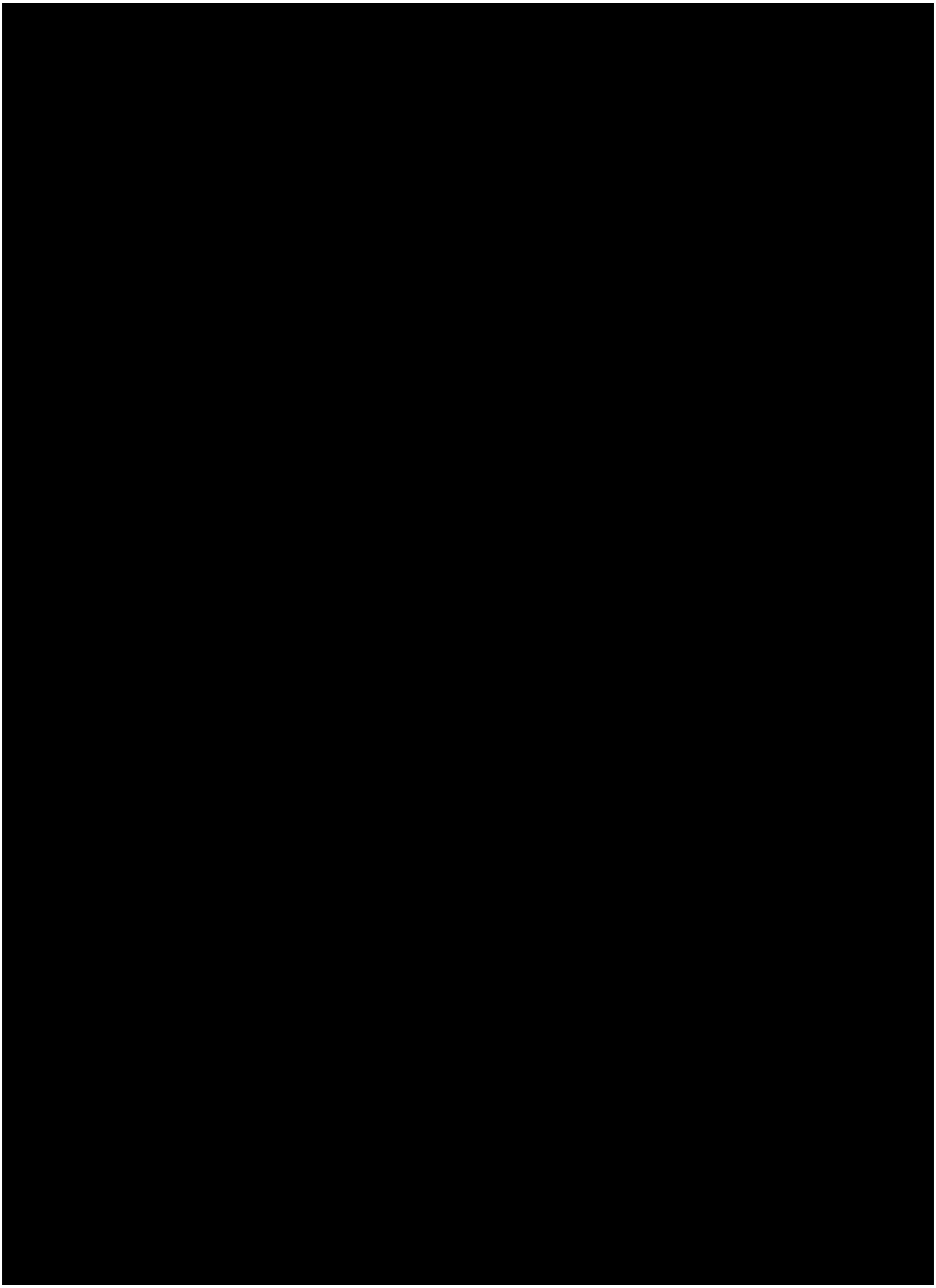
The primary endpoints will be summarized by age (< 40 years, ≥ 40 years). In addition, due to the potential for different vaccine titer responses from different vaccine manufacturers, each primary vaccine response endpoint will also be summarized by the corresponding vaccine brand names.

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

5.1.1 Primary Endpoints

[redacted]



[redacted]

5.1.2 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), and up to the End of Study (EOS) date.

Treatment-emergent Serious Adverse Event (TESAE)

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

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.

Tetanus Vaccine-related TEAE

A TEAE with the indicator flag "Is there a reasonable possibility that the event may have been caused by the Tetanus vaccine" equal to "Yes" on the Event eCRF.

Meningococcal Vaccine-related TEAE

A TEAE with the indicator flag "Is there a reasonable possibility that the event may have been caused by the Meningococcal vaccine" equal to "Yes" on the Event eCRF.

[redacted]

5.1.3 Exploratory Efficacy Endpoints

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.

Validated Investigator's 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 ≥ 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]

[redacted]

5.2 Study Dates

Informed Consent Date

The date on which subject signs the informed consent form.

Randomization Date

The date when subject was randomized to a treatment group.

First Investigational Product Dose Date

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

Last Investigational Product Dose Date

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 9.5.2).

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 24/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

Baseline Assessment

Baseline assessment for the endpoint of the interest, excluding vaccine response endpoints, is defined as the last nonmissing measurement taken 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, antibody and ECG where the collection time of the baseline assessment must not be later than time of the first dose of investigational product administration. For subjects who are randomized but not dosed after the randomization, the baseline of the study is defined as the last nonmissing measurement prior to or on the date of randomization.

Baseline assessment for the vaccine response endpoints is defined as the vaccine IgG antibody samples with nonmissing measurement at week [redacted] which should be collected prior to vaccine administration at week [redacted]

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.

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.

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 Calculation

Duration of Investigational Product Exposure (Days)

If subject 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 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

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.

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 (ie, number of at-risk subjects). Subjects with multiple occurrences of the same event will only be counted once.

Concomitant Therapy Used 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 24 visit will not impact the exploratory efficacy assessment.

Concomitant therapy for AD during the 24-week treatment period, not including safety follow-up period after Week 24 visit, includes medications with a start date within the range of Study Day 1 through

- the Study Day corresponding to the Week 24 assessment date for subjects with last efficacy assessment in WEEK 24 analysis window; or
- the earlier of (EOS Study Day, data cutoff – Study Day 1 + 1, or Day 169 [target day of WEEK 24 analysis visit window]) for subjects with last efficacy assessment before WEEK 24 analysis visit window.

6. Analysis Sets

Due to site-wide serious breach and GCP violations, all data from site 66091 will be excluded from all vaccine, efficacy and safety analyses to eliminate potential risk of obscuring the overall study results. All references of “randomized subjects” (including “full analysis set”, “safety analysis set”, and “immune response analysis set”) below will implicitly exclude the subjects from site 66091. The overall validity and scientific value of the study should not be impacted given the remaining sample size resulting from site exclusion is consistent with the planned sample size of 195. Key vaccine, efficacy, and safety data from site 66091 will be summarized or listed separately.

6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects. Subjects will be analyzed according to the randomized treatment. Analyses of disposition, demographic and baseline data, Important Protocol Deviations (IPDs), exploratory efficacy endpoints will utilize this analysis set.

6.2 Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who receive at least 1 dose of investigational product. Subjects will be analyzed based on the actual treatment received, where subjects who received at least 1 dose of rocatinlimab will be analyzed in the rocatinlimab treatment group regardless of the randomized treatment. Analyses of safety endpoints except for tetanus vaccine-related and meningococcal vaccine-related

TEAE endpoints, summary of investigational product administration, and summary of number of subjects received vaccine at week [redacted] will utilize this analysis set.

The tetanus vaccine-related TEAE endpoints will be assessed based on a subset of subjects in the Safety Analysis Set who received the tetanus vaccine administration. Similarly, the meningococcal vaccine-related TEAE endpoints will be assessed based on a subset of subjects in the Safety Analysis Set who received the meningococcal vaccine administration.

6.3 Immune Response Analysis Sets

Two Immune Response Analysis Sets (IRAS) will be defined for the tetanus vaccine and meningococcal vaccine separately for the evaluation of the primary endpoints. Each IRAS includes a subset of subjects in the safety analysis set who are evaluable for the respective vaccine response. Subjects eligible for vaccine response evaluation must not miss more than one dose of investigational product prior to vaccine administration at week [redacted] The vaccine should be administered no later than 56 days after the last dose of investigational product prior to week [redacted] to ensure steady-state investigational product concentrations are maintained during vaccine administration.

Subjects are considered evaluable for the tetanus vaccine response if all the following criteria are met:

- had week [redacted] vaccine IgG antibody sample collected before vaccine administration
- received the vaccine administration at week [redacted]
- prior to the week [redacted] visit, received last investigational product dose at week [redacted] or week [redacted] within 56 days prior to vaccine administration, and did not miss more than one dose
- had week 24 vaccine IgG antibody sample collected within 21 and 56 days after vaccine administration
- had antitetanus IgG antibody results at both week [redacted] and week 24

Subjects are considered evaluable for the meningococcal vaccine response if all the following criteria are met:

- had week [redacted] vaccine IgG antibody sample collected before vaccine administration
- received the vaccine administration at week [redacted]
- prior to the week [redacted] visit, received last investigational product dose at week [redacted] or week [redacted] within 56 days prior to vaccine administration, and did not miss more than one dose

- had week 24 vaccine IgG antibody sample collected within 21 and 56 days after vaccine administration
- had antimeningococcal IgG antibody results at both week [redacted] and week 24

Subjects will be analyzed according to the actual treatment received.

7. Planned Analyses

7.1 Primary Analysis

The primary analysis will be conducted when all subjects have completed the week 24/EOT visit, and the data have been entered, cleaned, and locked. The objective of the primary analysis is to assess vaccine response and complete efficacy and safety data through week 24 and additional safety data available only for subjects who do not enroll in the long-term maintenance study.

7.2 Final Analysis

The final analysis will be conducted at the end of the study when all subjects 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 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, PK, 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 primary endpoints will not be imputed.

Missing data in exploratory 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 [redacted] 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.

For antitetanus and antimeningococcal IgG antibody assessments, please refer to Section 5.1.1 for imputation steps.

Missing and incomplete dates in AE, concomitant medication and procedures 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 vaccine response and 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 distribution of vaccines from different manufacturers with different vaccine titer responses are not balanced between the treatment groups

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

No endpoints will be analyzed that require a specific distribution assumption.

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

Statistical analyses in this study will be descriptive in nature. No formal hypothesis will be tested in this study.

Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively by the randomized treatment. For categorical endpoints, the descriptive statistics will contain [redacted] For continuous endpoints, the descriptive statistics will include [redacted].

9.2 Subject Accountability

The number and percent of subjects who were randomized, received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing, completed study, discontinued study and reasons for discontinuing will be summarized.

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 percent 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. If multiple races have been reported for a subject, the subject 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)
- Stratification factor (severity of disease)
- Medical history
- Selected clinical outcome assessment (COA)/patient-reported outcome (PRO) at baseline

9.5 Primary and Exploratory Efficacy Analyses

9.5.1 Analyses of Primary Endpoints

Positive antitetanus response at week 24 and positive antimeningococcal response at week 24 are binary endpoints. For between rocatinlimab mg and placebo

and [redacted] will be provided. Treatment comparisons will be based on [redacted]. Analyses of vaccine response endpoints will be based on the respective IRAS, which will only include subjects with observed data (Section 6.3). Hence, missing data imputation is not applicable. Subjects who are excluded from the respective IRAS will also be summarized by the exclusion reasons.

9.5.2 Analyses of Exploratory Efficacy Endpoints

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 complete all remaining study visits and procedures with the exception of investigational product administration and postdose monitoring procedures through week 24 after permanent discontinuation of investigational product for evaluation of endpoints.

According to the clinical questions of interest, the primary estimand for each binary exploratory endpoint (Section 2.1) is to measure the effect of rocatinlimab [redacted] 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 (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. Remaining missing data after applying the strategy for each intercurrent event will be imputed using [redacted]

Each binary exploratory endpoint will be assessed descriptively, including the frequency, percentage, and [redacted] (moderate [vIGA-AD score =3] versus severe [vIGA-AD score = 4]).

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

No safety endpoints are considered primary endpoints.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

Subject incidence of all TEAE, TESAE, TEAE leading to discontinuation of investigational product, treatment-related TEAE, tetanus vaccine-related TEAE, meningococcal vaccine-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 be limited to infections, injection-related reactions, injection site reactions, hypersensitivity reactions, major adverse cardiovascular events (MACE), malignancy, neuropsychiatric events, aphthous ulcers, conjunctivitis, and gastrointestinal ulceration/perforation.

Subject 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 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 (> 1.5x ULN)

9.6.4 Vital Signs

The analyses of vital signs will include summary statistics over time by treatment group. 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 bmp

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]

9.6.7 Antibody Formation

The incidence and percentage of subjects who develop [redacted] at any time will be tabulated by treatment group.

A listing of antirocatinlimab antibody results for all timepoints tested for each subject with positive antirocatinlimab antibodies at any time will be reported.

9.6.8 Exposure to Investigational Product

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

9.6.9 Exposure to Concomitant Medication

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

9.7 Other Analyses

9.7.1 Analyses of Pharmacokinetic Endpoints

The PK samples will be analyzed only for those subjects assigned to a rocatinlimab treatment group. All PK-related tables, figures, listings and other deliverables will be generated by [redacted]

10. Changes From Protocol-specified Analyses

[redacted]

11. Literature Citations / References

Merola J.F., Bagel J., Almgren, P., Ropke, M.A., Lophaven, K.W., Vest, N.S., and Grewal, P. Tralokinumab does not impact vaccine-induced immune responses: Results from a 30-week randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. (2021). *J Am Acad Dermatol*, 85(1), 71-78.

Klingenberg, B. A new and improved confidence interval for the Mantel-Haenszel risk difference (2014). *Statistics in Medicine*, 33(17), 2968-2983.

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]

Above analyses will be conducted by [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 Medications 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)	[redacted]
Topical corticosteroids (TCS)	

Medication of Interest (MOI) Category	Definition
	[redacted]
Topical PDE4 inhibitors	
Topical JAK inhibitors	
Other topical therapy	
Emollients	
Systemic Therapies	
Phototherapies	
Systemic PDE4 inhibitors	

Medication of Interest (MOI) Category	Definition
Systemic corticosteroids	[redacted]
Conventional Immunosuppressants	
Biologics	

Medication of Interest (MOI) Category	Definition
	[redacted]
Systemic JAK inhibitors	

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 'BEFORE' if the imputed start date is prior to the first dose date; else 'DOUBLE-BLIND'. For subjects who did not receive investigational product, the imputed start date will be compared with the randomization date.

Derivation Rules for Medication and Procedure End Interval

Medication and procedure end interval will be set to 'BEFORE' if the imputed start date is prior to the first dose date; else 'DOUBLE-BLIND'. 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
Partial: yyyy	< first dose date yyyy	BEFORE
	≥ first dose date yyyy	DOUBLE-BLIND
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 24 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 24 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 [redacted]

Table 13-1 Analysis Visit Window for Endpoints Based on Data Collection at Site Visits Excluding Vaccine IgG Antibody Sample

Analysis Visit	Target Day	Visit Window (Study Day)
BASELINE	1	See Baseline Assessment definition in Section 5.3
WEEK [redacted]	15	2 to 22 for efficacy endpoints Or Day 1 post dose to 22 for safety related endpoints
WEEK [redacted]	29	23 to 43
WEEK [redacted]	57	44 to 71
WEEK [redacted]	85	72 to 99
WEEK [redacted]	113	100 to 127
WEEK [redacted]	141	128 to 155
WEEK 24	169	≥ 156
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 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 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	[redacted]
Injection-related Reactions	Injection-related reactions	
	Hypersensitivity reactions	
Injection site reactions	N/A	
Infections	All infections	
	Serious infections	
	Tuberculosis	
	Opportunistic infections	
	Infections requiring systemic antibiotic therapy	
	COVID-19	
Malignancy	N/A	
Neuropsychiatric events	Depression (excluding suicide and self-injury)	
	Suicidal ideation and behavior	
	Psychosis and psychotic disorders	
Conjunctivitis	N/A	
Aphthous ulcers	N/A	
Gastrointestinal ulceration, hemorrhage, or perforation	N/A	
	MACE	

Major Category	Sub-category	Search Strategy or Definition
Cardiovascular events		[redacted]
	Extended MACE	
	Other cardiovascular events	

Major Category	Sub-category	Search Strategy or Definition
		[redacted]
	All positively adjudicated serious cardiovascular events	

Appendix F. Sample SAS Code for Primary and Exploratory Efficacy Analyses