Title Page

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
Investigational Product:		Rocatinlimab (AMG 451)
Trade Name:		Not applicable
Sponsor	**Name of Sponsor:**	Amgen, Inc.
	Address:	One Amgen Center Drive Thousand Oaks, CA, 91320
	Telephone Number:	+1 805-447-1000
Protocol Approver	**Name:**	[redacted], MD, MBA
	Function:	VP Global Development
Key Sponsor Contact	**Name:**	[redacted], MD, LLB, PhD
	Address:	One Amgen Center Drive Thousand Oaks, CA 91320
	Telephone Number:	[redacted]
	Email Address:	
EudraCT/EU CT Number:		Not applicable
Pediatric Investigational Plan Number		Not applicable
NCT Number:		**NCT05899816**
Protocol Version Date:		**Document Version** **Date**

	Original **Superseding Original** **Amendment 1**	25 January 2023 14 April 2023 **30 June 2023**
Data Elements Standards Version:	8	

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (International Council for Harmonisation [ICH] E6).

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1- 800-77-AMGEN; Canadian sites, 1-866-50-AMGEN; Amgen's general number in the US, 1-805-447-1000.

Investigator's Agreement:

I have read the attached protocol entitled 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), dated **30 June 2023**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

_____
Title and Role of Investigator

_____
Institution Name

_____
Address and Telephone Number of Institution

Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1 Synopsis

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)

Study Phase: 3

Indication: Moderate-to-severe Atopic Dermatitis (AD)

Study Rationale

Atopic dermatitis (AD) is a chronic relapsing and remitting, inflammatory skin disease dominated by reactive T helper type 2 (Th2) cells. The proximate pathophysiologic mechanism for eczematous lesions is now understood to be largely due to inflammation related to dysregulation of Th2 cells (Guttman-Yassky, 2018). OX40 (CD134) is expressed predominantly on T-cells, including effector cells, shortly after their activation (Croft, 2010). OX40 and its ligand, OX40L, are crucial for the generation of Th2 memory cells, and may thus play a central role in the pathogenesis and chronicity of AD (Sitrin et al, 2017). Blocking OX40 signaling has resulted in inhibition of T-cell responses and pathogenic symptoms in animal models of autoimmune diseases (Salek-Ardakani and Croft, 2006; Croft et al, 2009). Rocatinlimab (formerly known as AMG 451 and KHK4083) is a human, afucosylated, immunoglobulin G1 (IgG1) monoclonal antibody that binds and inhibits the OX40/OX40L interaction, and thereby, suppresses clonal T-cell expansion. In a phase 2 study (Study 4083-006) evaluating the efficacy, safety, and tolerability of repeated doses of rocatinlimab in subjects with moderate-to-severe AD, and conducted by Amgen partner Kyowa Kirin Co., Ltd, statistically significant improvements in percent change from baseline to week [redacted] in Eczema Area and Severity Index (EASI) score was observed in all rocatinlimab-treated cohorts versus placebo. In this study, the [redacted] mg every 2 weeks (Q2W) dose was well tolerated with an acceptable adverse event profile.

Rocatinlimab targets a pathway for T cell activation, and it is not known whether rocatinlimab impacts the response to vaccines. Since vaccination programs are an important part of health maintenance and globally recommended, it is relevant to

investigate if rocatinlimab affects development of vaccination-induced immune responses.

This trial will assess the development of immunization responses against 2 vaccines (tetanus vaccine and meningococcal vaccine) in adults with moderate-to-severe AD who are treated with rocatinlimab. These 2 standard vaccines have been selected to enable a broader assessment of the effect of rocatinlimab on immune activation. The selected types of vaccines are known to result in an immune response involving both T- and B-cells as well as other key cell types of the immune system. Tetanus vaccine is considered as a T-cell dependent vaccine by which protective immunoglobulin G (IgG) antibody is produced through T-cell activation immunity and meningococcal vaccine (eg, meningococcal polysaccharide vaccine [MPSV4]) is a polysaccharide vaccine which is considered to elicit its humoral immunity and B-cell activation independent of T-cell (Leo et al, 2011 and Blauvelt et al, 2019).

Benefit/Risk Assessment

In the phase 2b Study 4083-006, 3 dose levels and 2 dosing frequencies ([redacted] mg [redacted] [redacted]], [redacted] mg [redacted] 300 mg Q2W, and [redacted] mg Q2W) were tested in subjects with moderate to severe AD. All doses were associated with improved Investigator's Global Assessment (IGA) and achievement of ≥ 75% reduction from baseline in EASI score (EASI 75) responses compared with placebo.
Rocatinlimab has been generally well tolerated and no adverse events with fatal outcome attributed to rocatinlimab have been reported in the completed studies.

[redacted]

Only the **SC** route of administration is planned, which limits the risk of adverse effects **associated with** IV infusion**. Overall, SC administration** is associated with a lower incidence of systemic reactions and/or lower severity of acute reactions that tend to be local (Mateos et al, 2020; Davies et al, 2017; Assouline et al, 2016). Eligibility criteria have been implemented to exclude subjects vulnerable to acute allergic reactions and infections. **A**ll subjects will be observed after investigational product administration and will be monitored throughout the study **with hematology and standard adverse event and serious adverse event reporting**.

Overall, the above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure for further data on rocatinlimab.

Objective(s) and Endpoint(s)/Estimand(s)

Objectives	Endpoints
Primary	
• To estimate vaccine response in rocatinlimab group vs placebo group, assessed using antibody anti-tetanus response at week 24	• Positive anti-tetanus response at week 24 defined as the antibody response to tetanus vaccine assessed by measuring serum anti-tetanus immunoglobulin G (IgG) by an immunoassay
• To estimate vaccine response in rocatinlimab group vs placebo group, assessed using antibody anti-meningococcal response at week 24	• Positive anti-meningococcal response at week 24 defined as the antibody response to meningococcal vaccine assessed by measuring serum anti-meningococcal IgG by an immunoassay
Safety and Immunogenicity	
• To characterize the safety and tolerability of rocatinlimab in the proposed population	• Treatment-emergent adverse events and serious adverse events
[redacted]	

Overall Design

This is a phase 3, 24-week, double-blind study to evaluate the efficacy of anti-tetanus and anti-meningococcal vaccination in rocatinlimab-treated adult subjects with

moderate-to-severe AD. Previous biologic or targeted-small molecules (eg, Janus kinase [JAK] inhibitors) use is allowed with an adequate washout period. Approximately [redacted] eligible subjects will be randomized [redacted] to either rocatinlimab [redacted] mg SC [redacted] for 24 weeks with a loading dose at week [redacted] or placebo [redacted] for a duration of 24 weeks with a loading dose at week [redacted] Randomization will be stratified by baseline disease severity (moderate [vIGA-AD score = 3] versus severe [vIGA-AD score = 4]). Subjects will undergo a screening visit to confirm eligibility requirements. The screening period, which starts with the initial screening visit and ends with the day 1 prerandomization visit, will be a minimum of [redacted] days **(inclusive)** and a maximum of [redacted] days. At the day 1 prerandomization visit, subjects who meet all eligibility criteria will be randomized.

Subjects who do not meet all eligibility requirements at screening and/or day 1 prerandomization visits will be considered screen failures. Subjects may be allowed to rescreen once.

Tetanus and meningococcal vaccines will both be administered at the week [redacted] visit for each subject.

Treatment Period

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

At a subset of sites, subjects will have the option to participate in the [redacted] for exploratory purposes. Subjects in this **sub**study will be asked to **complete daily electronic diary (eDiary) and** wear an activity monitor to measure their activity and sleep up to week 24. Subjects are required to wear the device every day except when charging. The watch should be particularly worn before going to sleep and throughout the duration of sleep. The activity monitor generates data that is then captured by a mobile application on the study provided mobile device. Participants will be instructed to wear the activity monitor on their non-dominant wrist and use the mobile device to upload the activity monitor data at home until the deployment period is completed. Refer to **Section 8.4.2 for more details on the eDiary data collection and** [redacted].

Concomitant Use of TCS/TCI

Topical corticosteroids (TCS) of low to medium potency with or without topical calcineurin inhibitors (TCI) will be considered adjunctive therapy, which could be tapered or stopped and restarted, as clinically required at the discretion of the investigator, during the study.

Rescue Therapies for AD

Use of TCS of high or super-high potency, topical phosphodiesterase type 4 (PDE4) inhibitors, oral or topical JAK inhibitors, phototherapy, **or systemic therapies for AD** during the 24-week treatment period will be considered use of rescue therapy in the analysis (Table 6-3). Allowed rescue therapies are those approved for treatment of AD as well as local standard of care. **Subjects may continue investigational product if there is concurrent use of topical rescue therapies (excluding topical JAK inhibitors), or phototherapy. Subjects may require temporary interruption of investigational product if systemic corticosteroids are used for ≤ 2 consecutive weeks to avoid concurrent administration with investigational product. Subjects must permanently discontinue investigational product if there is use of specific prohibited therapies: systemic corticosteroids for > 2 consecutive weeks, conventional non-biologic, non-targeted immunosuppressive systemic therapies, biologics, targeted systemic AD rescue therapies, or topical JAK inhibitors (see Table 6-2 and Table 6-3 for additional details).**

Discontinuation of Study Treatment and Subject Discontinuation

Subjects who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures through week 24**,** which will correspond to their EOT visit, **including the vaccine administrations at week** [redacted] **and the vaccine response assessment at 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 who permanently discontinue investigational product and do not complete the remaining study visits through week 24 should complete the EOT visit at the next scheduled visit following the last dose of the investigational product.

Subjects who do not permanently discontinue investigational product through week 24 due to safety-related reasons or protocol-defined stopping rules will be eligible to enroll in the long-term maintenance study (Study [redacted]).

Safety Follow-up

An SFU visit is required [redacted] after the last dose of investigational product for all subjects who do not enroll into the long-term maintenance study.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

Number of Subjects

A total of [redacted] subjects will be randomized in [redacted] ratio to rocatinlimab [redacted] mg (N = [redacted]) and placebo (N = [redacted]).

A maximum of up to [redacted] subjects will be included in in the [redacted]

Summary of Subject Eligibility Criteria

- Age 18 to 54 years with a diagnosis of AD (according to the American Academy of Dermatology Consensus Criteria; Eichenfield, 2014), that has been present for at least **12** months before the date of informed consent.
- History of inadequate response to **TCS** of medium-potency or high-potency (with or without **TCI** as appropriate) or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks).

[redacted]

For a full list of eligibility criteria, please refer to Sections 5.1 to 5.2.

Treatments

Subjects will be randomized in [redacted] ratio to receive:

Amgen Investigational Product: Rocatinlimab [redacted] mg

Placebo

For full understanding of the study treatment groups, see Study Schema below (Figure 1-1).

Statistical Considerations

A total of [redacted] subjects will be randomized in [redacted] ratio to 2 treatment groups as follows:

- Rocatinlimab [redacted] mg (N = [redacted])
- Placebo (N = [redacted]).

The analyses will be descriptive in nature; therefore, the sample size is based on the [redacted].

A sample size of [redacted] is planned. [redacted]

Planned Analyses

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 complete efficacy and safety data through week 24 and additional safety data available during SFU as of the data cutoff date.

Primary endpoints

Positive anti-tetanus response at week 24 and positive anti-meningococcal response at week 24 are binary endpoints. The difference in response rates between the treatment groups (rocatinlimab – placebo) will be calculated using the Mantel-Haenszel estimate of the risk difference stratified by the randomization strata together with the 95% CI.

The primary analysis of the primary endpoints will be analyzed using the respective immune response analysis set (IRS) including all randomized subjects who received at least 1 dose of investigational product, vaccine injection of the interest at week [redacted] and had measurement response to vaccine at **week [redacted] and** week 24.

Safety Analyses

Subject incidence of all treatment-emergent adverse events will be tabulated by treatment group and by system organ class, preferred term, and worst grade of severity. Summary tables of fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product, treatment-related adverse events, and

events of interest will also be provided. Subject incidence of device-related adverse events, if applicable, may also be provided by system organ class and preferred term.

The analysis of safety laboratory results will include summary statistics over time by treatment group. Shifts in grades of selected safety laboratory values between baseline and the worst on-study value will be tabulated by treatment group, as applicable.

The analysis of vital signs will include summary statistics of change from baseline over time by treatment group. Shifts in vital sign values between baseline and the worst on-study value will be tabulated by treatment group.

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

For a full description of statistical analysis methods, please refer to Section 9.

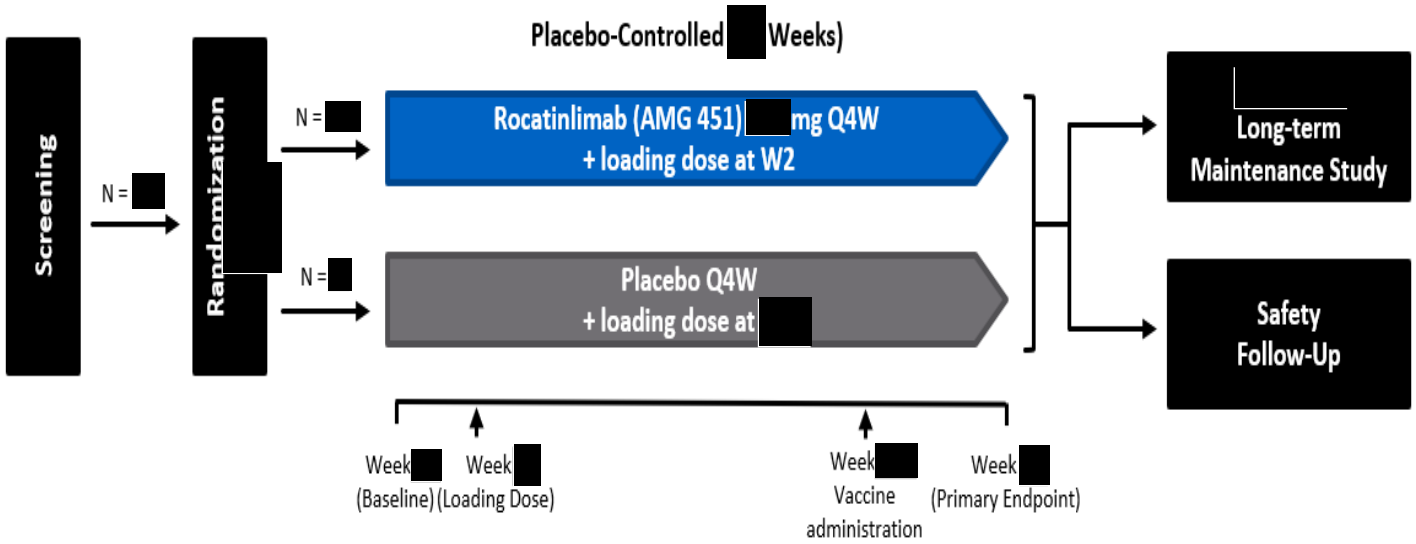
Statistical Hypotheses

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

Sponsor Name: Amgen, Inc.

1.2 Study Schema

Figure 1-1. Study Schema



N = total number of **subjects**; ; .

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities

Procedure	Screening (Up to [redacted] Days)[a]		Treatment Period[b]									
	Initial Screening	Day 1 Prerand	Day 1 Postrand[c]	[redacted]								Unsched Visit[v]
GENERAL AND SAFETY ASSESSMENTS												
Informed consent	X											
Inclusion and exclusion criteria	X	X[c]										
Demographics	X											
Physical examination[bb]	X						X			X	X	
Vital signs[e]	X		X	X	X	X	X	X	X	X	X	X
Height	X											
Body weight	X											
Medical history	X											
Cardiovascular medical history	X											
Dermatologic medical history	X											
Immunologic medical history	X											
Medication history	X											
[redacted]												
Substance use history[g]	X											
[redacted]												
ECG	X						**X**			X		**X**

Page 1 of 5

Footnotes defined on last page of this table.

Table 1-1. Schedule of Activities

Procedure	Screening (Up to [redacted] Days)[a]		Treatment Period[b]									
	Initial Screening	Day 1 Prerand	[redacted]									Unsched Visit[v]
Cardiovascular risk factors			X									
Adverse events			X	X	X	X	X	X	X	X	X	X
Serious adverse events[i]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies review	**X**	**X**	X	X	X	X	X	X	X	X	X	X
[redacted]												
Screening TB risk assessment questionnaire		**X**										
On study TB risk assessment questionaire[o]							X			X	X	
LABORATORY ASSESSMENTS[k]												
Coagulation	X											X[v]
HIV, Hepatitis B and C screening[l]	X											X
Hepatitis B DNA (reactivation monitoring only)[aa]										**X**		**X**
Serum pregnancy test (females **of child-bearing potential** only)[m]	X											X[v]
Urine pregnancy test (females **of child-bearing potential** only)[m]		X			X	X	X	X	X	X	X	X[v]
Hematology	X		X		X	X		X		X	X	X[v]
Chemistry	X		X			X		X		X	X	X[v]
Urinalysis[n]	X											X[v]

Footnotes defined on last page of this table.

Table 1-1. Schedule of Activities

Procedure	Screening (Up to [redacted] Days)[a]		Treatment Period[b]									
	Initial Screening	Day 1 Prerand	[redacted]									Unsched Visit[v]
QuantiFERON GOLD[o]	X										X	X[v]
Tetanus IgG antibody levels									X[x]	X		
Meningococcal IgG antibody levels									X[x]	X		
[redacted]												
EFFICACY/CLINICAL OUTCOME ASSESSMENTS – ASSESSED BY INVESTIGATOR USING E-TABLET												
vIGA-AD™	X	X					X	X		X		X[w]
AD morphology assessment[p]							X	X		X		X[w]
EASI			X				X	X		X		X[w]
[redacted]												
EFFICACY/CLINICAL OUTCOME ASSESSMENTS – ASSESSED BY SUBJECT USING E-TABLET												
HADS	X	X		X	X	X	X	X	X	X	X	**X[d]**

Footnotes defined on last page of this table.

Table 1-1. Schedule of Activities

Procedure	Screening (Up to [redacted] Days)[a]		Treatment Period[b]									
	Initial Screening	Day 1 Prerand	[redacted]									Unsched Visit[u]
STUDY TREATMENT												
Randomization			X									
Mental Health recommendation review[cc]		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**		
[redacted]												
EFFICACY/CLINICAL OUTCOME ASSESSMENTS – ASSESSED BY SUBJECT USING E-DIARY												
Site assigns e-diary	X											
Worst pruritus NRS[q, r]	←----------Daily e-Diary----------→											
AD skin pain NRS[r]	←----------Daily e-Diary----------→											
Sleep disturbance NRS[r]	←----------Daily e-Diary----------→											
Sleep assessments[r]	←----------Daily e-Diary----------→											

Footnotes defined on last page of this table.

Table 1-1. Schedule of Activities

Procedure	Screening (Up to [redacted] Days)[a]		Treatment Period[b]									
	Initial Screening	Day 1 Prerand	[redacted]									Unsched Visit[uv]
EFFICACY/CLINICAL OUTCOME ASSESSMENTS – ASSESSED BY INVESTIGATOR USING E-TABLET												
SCORAD (investigator-facing)			X	X	X	X	X	X	X	X		
EFFICACY/CLINICAL OUTCOME ASSESSMENTS – ASSESSED BY SUBJECT USING E-TABLET												
POEM			X	X	X	X	X	X	X	X		
PGI-S			X	X	X	X	X	X	X	X		
PGI-C				X	X	X	X	X	X	X		
SCORAD (subject-facing)			X	X	X	X	X	X	X	X		

AD = atopic dermatitis; [redacted]; D = day; DNA = deoxyribonucleic acid; EASI = Eczema Area and Severity Index; [redacted]; ECG = electrocardiogram; [redacted]; HADS = Hospital Anxiety and Depression Scale; HIV = human immunodeficiency virus; IgG = immunoglobulin G; JAK = Janus kinase; NRS = numeric rating scale; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; [redacted]; POEM = Patient Oriented Eczema Measure; SCORAD = severity scoring of atopic dermatitis; SFU = safety follow-up; TB = tuberculosis; TCI = topical calcineurin inhibitors; [redacted]; Unsched = unscheduled; vIGA-AD™ = Validated Investigator's Global Assessment for Atopic Dermatitis; W = week

[a] The screening period, which starts with the initial screening visit and ends with the day 1 prerandomization visit, will be a minimum of [redacted] days **(inclusive)** and a maximum of [redacted] days. At the day 1 prerandomization visit, subjects who meet all eligibility criteria will be randomized.

[b] Subjects who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures through week 24, **including the vaccine administrations at week [redacted] and the vaccine response assessment at week 24,** for the evaluation of the primary endpoints. Subjects who permanently discontinue investigational product and do not complete the remaining study visits through week 24 should complete the EOT visit (see [redacted] in Table 1-1) at the next scheduled visit following the last dose of the investigational product. A safety follow-up visit is required [redacted] after the last dose of investigational product for all subjects who do not enroll into the long-term maintenance study (Study [redacted]

[c] Only certain eligibility criteria will be re-evaluated at the day 1 prerandomization visit. These criteria are required to be met for enrollment/randomization. All baseline assessments at day 1 postrandomization visit must be completed prior to administration of investigational product.

[redacted]

[e] Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature measured before investigational product administration.

[redacted]

[g] Alcohol, recreational drugs, and tobacco use.

[redacted]

[i] Once the study has ended, the investigator will report to Amgen immediately and no later than 24 hours following the investigator's awareness of the event, any serious adverse event(s) suspected to be related to the investigational product that they become aware of. Refer to Section 8.5.6 for additional details.
[j] Can be performed at a later timepoint during the study if not previously performed.
[k] To be collected predose.
[l] Hepatitis B DNA testing may be performed at subsequent visits at the discretion of the investigator.
[m] Additional on-study pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
[n] Additional urinalysis can be performed on-study at the investigator's discretion per standard of care.
[o] Refer to Section 8.10.1 for additional information on TB assessments.
[p] Only for subjects who achieve vIGA-AD score of 1.
[q] This screening assessment will be collected using the site tablet at the initial screening visit and will have a 7-day recall. Throughout the rest of the study, the daily recall NRS will be collected on the subject's handheld device.
[r] Daily diary entries to begin the day after the initial screening visit through [redacted] visit.
[s] Subjects must be monitored for 2 hours following **at least** the first **2 doses** of investigational product **at day 1** and **week** [redacted] **treatment period. If no systemic injection-related reactions, including immediate type hypersensitivity reactions, are observed after the first 2 doses, the post-dose monitoring period may be reduced to at least** 30 minutes **for** subsequent **open-label doses. If systemic injection-related reactions are observed after the first 2 doses, the 2-hour post-dose monitoring period will remain as needed.** Refer to Section **8.4.2** for additional information on post-dose monitoring.
[t] Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature measured at the end of the 2-hour post-dose monitoring period before subject is discharged. **[X] as needed.**
[u] Unscheduled visits may occur at any timepoint during the treatment period.
[v] Laboratory assessments may be completed at unscheduled visits at the investigator's discretion.
[w] Efficacy/clinical outcome assessments at unscheduled visits are optional and may be performed at the discretion of the investigator.
[x] Samples at [redacted] should be collected prior to vaccine administration.
[redacted]

[aa] For subjects with positive HBsAg and/or HBV core Ab at initial screening. Any additional testing may be performed per investigator's discretion.
[bb] Complete physical examination will be conducted at screening, and symptom-directed physical examination at subsequent study visits at the discretion of the investigator per standard of care. Refer to Section 8.2.4 for additional information.
[cc] Investigator must review latest recommendation prior to enrollment and/or dosing.

2. Introduction

2.1 Study Rationale

Atopic dermatitis (AD) is a chronic relapsing and remitting, inflammatory skin disease dominated by reactive Th2 cells. The proximate pathophysiologic mechanism for eczematous lesions is now understood to be largely due to inflammation related to dysregulation of Th2 cells (Guttman-Yassky, 2018). OX40 (CD134) is expressed predominantly on T-cells, including effector cells, shortly after their activation (Croft, 2010). OX40 and its ligand, OX40L, are crucial for the generation of Th2 memory cells, and may thus play a central role in the pathogenesis and chronicity of AD (Sitrin et al, 2017). Blocking OX40 signaling has resulted in inhibition of T-cell responses and pathogenic symptoms in animal models of autoimmune diseases (Salek-Ardakani and Croft, 2006; Croft et al, 2009). Rocatinlimab (formerly known as AMG 451 and KHK4083) is a human, afucosylated, immunoglobulin G1 (IgG1) monoclonal antibody that binds and inhibits the OX40/OX40L interaction, and thereby, suppresses clonal T-cell expansion. In a phase 2 study (Study 4083-006) evaluating the efficacy, safety, and tolerability of repeated doses of rocatinlimab in subjects with moderate-to-severe AD, and conducted by Amgen partner Kyowa Kirin Co., Ltd, statistically significant improvements in percent change from baseline to week [redacted] in Eczema Area and Severity Index (EASI) score was observed in all rocatinlimab-treated cohorts versus placebo. In this study, the [redacted] mg every 2 weeks (Q2W) dose was well tolerated with an acceptable adverse event profile.

Rocatinlimab targets a pathway for T cell activation, and it is not known whether rocatinlimab impacts the response to vaccines. Since vaccination programs are an important part of health maintenance and globally recommended, it is relevant to investigate if rocatinlimab affects development of vaccination-induced immune responses.

This trial will assess the development of immunization responses against 2 vaccines (tetanus vaccine and meningococcal vaccine) in adults with moderate-to-severe AD who are treated with rocatinlimab. These 2 standard vaccines have been selected to enable a broader assessment of the effect of rocatinlimab on immune activation. The selected types of vaccines are known to result in an immune response involving both T- and B-cells as well as other key cell types of the immune system. Tetanus vaccine is considered as a T-cell dependent vaccine by which protective IgG antibody is produced through T-cell activation immunity and meningococcal vaccine (eg, meningococcal

polysaccharide vaccine [MPSV4]) is a polysaccharide vaccine which is considered to elicit its humoral immunity and B-cell activation independent of T-cell (Leo et al, 2011 and Blauvelt et al, 2019).

2.2 Background

2.2.1 Disease

Atopic dermatitis (AD) is one of the most prevalent inflammatory skin diseases. It usually develops in childhood and may persist into adulthood; less frequently, it starts in midlife or late life (Barbarot et al, 2018). The disorder is characterized by recurrent, pruritic, localized eczema, often with seasonal fluctuations. Many patients also have allergic asthma, allergic rhino-conjunctivitis, food allergies, and other immediate hypersensitivity (type 1) allergies (Stander, 2021). The prevalence and incidence of AD have increased over the past several decades. **Globally, the** prevalence of **AD is up to** 10% among adults and up to 20% among children, making AD the 15th most common nonfatal disease and the skin disorder with the highest disease burden, in terms of disability-adjusted life-years (**Laughter et al, 2021; Stander, 2021**).

In clinical practice, AD is classified as mild, moderate, or severe based on a variety of clinical features, including severity of skin lesions and pruritus, and extent of disease (body surface area [BSA] involved). The goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations and minimize therapeutic risks (Eichenfield et al, 2014). Current AD therapeutic armamentarium includes emollients/skin care, topical or systemic corticosteroids, phototherapy, topical calcineurin inhibitors **(TCI)**, crisaborole, delgocitinib, systemic immunosuppressants, and biologics (Wollenberg et al, 2018). Patients with moderate-to-severe AD are often given topical treatments before or in conjunction with a systemic treatment or as maintenance therapy after tapering off systemic treatment.

Until recently, the lack of safe and effective systemic treatments meant that most patients with moderate-to-severe AD were not well controlled. Emerging, narrow targeting biologic agents blocking specific cytokine or cytokine receptors have shown significant clinical benefit in these patients. Dupilumab, a monoclonal antibody that binds to the interleukin 4Rα (IL-4Rα) subunit shared by the interleukin 4 (IL-4) and interleukin 13 (IL-13) receptor complexes, is the first biologic approved in the United States (US) for patients 6 months and older with moderate-to-severe AD, in the European Union for patients **12** years and older **with moderate-to-severe AD and patients 6 months to 11 years** with severe AD who are candidates for systemic

therapy, and in Japan for adults with moderate-to-severe AD. While dupilumab has shown favorable efficacy data in moderate-to-severe AD, nearly half of the patients receiving 300 mg every 1 or 2 weeks fail to reach EASI 75 at week [redacted] (Snast et al, 2018). Additionally, exacerbation or new onset head and neck dermatitis and conjunctivitis have been reported in up to 10% of adults on dupilumab after a median time of 65 days (Jo et al, 2021). Therefore, there is still a large unmet need for novel biologic therapies with different mechanism of action and with improved safety profile for this population.

2.2.2 Amgen Investigational Product Background

2.2.2.1 Rocatinlimab

Rocatinlimab is an investigational human, afucosylated IgG1 mAb specific for inhibiting OX40/OX40L interaction to treat the chronic inflammation in AD and other autoimmune diseases. To date, the efficacy and safety of intravenous (IV) and **subcutaneous (**SC**)** rocatinlimab has been evaluated in 5 early phase clinical studies.

A detailed description of the chemistry, pharmacology, efficacy, and safety of rocatinlimab is provided in the **i**nvestigator's **b**rochure **(IB)**.

2.2.2.2 Tetanus and Meningococcal Vaccines

This trial will assess the development of immunization responses against 2 vaccines: tetanus vaccine and meningococcal vaccine. These 2 standard vaccines have been selected to enable a broader assessment of the effect of rocatinlimab on immune activation. The tetanus and diphtheria (Td) vaccines (**for example** TENIVAC® and TDVAX®); tetanus, diphtheria, and pertussis (Tdap) vaccines (**for example** Adacel® and Boostrix®); and meningococcal vaccines (**for example** Menactra®, Menveo®, and MenQuadfi®) **that** are approved in the US for adult administration will be allowed **in the US** in this study. **Tetanus, Tdap and meningococcal vaccines that are approved in Canada are allowed in Canada in this study.** The selected types of vaccines are known to result in an immune response involving both T- and B-cells as well as other key cell types of the immune system. Tetanus vaccine is considered as a T-cell dependent vaccine by which protective IgG antibody is produced through T-cell activation immunity and meningococcal vaccine (eg, MPSV4) is a polysaccharide vaccine which is considered to elicit its humoral immunity and B-cell activation independent of T-cell (Leo et al, 2011 and Blauvelt et al, 2019).

2.3 Benefit/Risk Assessment

In the phase 2b Study 4083-006, 3 dose levels and 2 dosing frequencies ([redacted] mg [redacted] mg [redacted] 300 mg Q2W, and [redacted] mg Q2W) were tested in subjects with moderate to severe AD. All doses were associated with improved Investigator's Global Assessment (IGA) and achievement of ≥ 75% reduction from baseline in EASI score (EASI 75) responses compared with placebo.

Rocatinlimab has been generally well tolerated and no adverse events with fatal outcome attributed to rocatinlimab have been reported in the completed studies.

[redacted]

Only the SC route of administration is planned, which limits the risk of adverse effects **associated with** IV infusion**. Overall, SC administration** is associated with a lower incidence of systemic reactions and/or lower severity of acute reactions that tend to be local (Mateos et al, 2020; Davies et al, 2017; Assouline et al, 2016). Eligibility criteria have been implemented to exclude subjects vulnerable to acute allergic reactions and infections. **A**ll subjects will be observed after investigational product administration and will be monitored throughout the study **with hematology and standard adverse event and serious adverse event reporting**.

Overall, the above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the IB for further data on rocatinlimab.

2.3.1 COVID-19

Amgen closely monitors the coronavirus disease 2019 (COVID-19) pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, patient safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities.

Patients who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should contact the investigator to ensure appropriate care as well as documentation and management of study activities.

Amgen considers that it is important to continue the proposed development of rocatinlimab in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

Subjects enrolled in this study are permitted to receive vaccinations for COVID-19 as described in Section 6.8.2.

3. Objective(s) and Endpoint(s)/Estimand(s)

Objectives	Endpoints
Primary	
• To estimate vaccine response in rocatinlimab group vs placebo group, assessed using antibody anti-tetanus response at week 24	• Positive anti-tetanus response at week 24 defined as the antibody response to tetanus vaccine assessed by measuring serum anti-tetanus immunoglobulin G (IgG) by an immunoassay
• To estimate vaccine response in rocatinlimab group vs placebo group, assessed using antibody anti-meningococcal response at week 24	• Positive anti-meningococcal response at week 24 defined as the antibody response to meningococcal vaccine assessed by measuring serum anti-meningococcal IgG by an immunoassay
Safety and Immunogenicity	
• To characterize the safety and tolerability of rocatinlimab in the proposed population	• Treatment-emergent adverse events and serious adverse events
[redacted]	

Objectives	Endpoints
[redacted]	

4. Study Design

4.1 Overall Design

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

This is a phase 3, 24-week, double-blind study to evaluate the efficacy of anti-tetanus and anti-meningococcal vaccination in rocatinlimab-treated adult subjects with moderate-to-severe AD. Previous biologic or targeted-small molecules (eg, Janus kinase [JAK] inhibitors) use is allowed with an adequate washout period. Approximately [redacted] eligible subjects will be randomized [redacted] to either rocatinlimab [redacted] mg SC [redacted] for 24 weeks with a loading dose at week [redacted] or placebo [redacted] for a duration of 24 weeks with a loading dose at week [redacted] Randomization will be stratified by baseline disease severity (moderate [vIGA-AD score = 3] versus severe [vIGA-AD score = 4]). Subjects will undergo a screening visit to confirm eligibility requirements. The screening period, which starts with the initial screening visit and ends with the day 1 prerandomization visit, will be a minimum of [redacted] days **(inclusive)** and a maximum of [redacted] days. At the day 1 prerandomization visit, subjects who meet all eligibility criteria will be randomized.

Subjects who do not meet all eligibility requirements at screening and/or day 1 prerandomization visits will be considered screen failures. Subjects may be allowed to rescreen once.

Tetanus and meningococcal vaccines will both be administered at the [redacted] visit for each subject.

Treatment Period

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

At a subset of sites, subjects will have the option to participate in the [redacted] for exploratory purposes. Subjects in this **sub**study will be asked to **complete daily electronic diary (eDiary) and** wear an activity monitor to measure their activity and sleep up to week 24. Subjects are required to wear the device every day except when charging. The watch should be particularly worn before going to sleep and throughout the duration of sleep. The activity monitor generates data that is then captured by a mobile application on the study provided mobile device. Participants will be instructed to wear the activity monitor on their non-dominant wrist and use the mobile device to upload the activity monitor data at home until the deployment period is completed. Refer to **Section 8.4.2 for more details on the eDiary data collection and** [redacted].

Concomitant Use of TCS/TCI

Topical corticosteroids (TCS) of low to medium potency with or without topical calcineurin inhibitors (TCI) will be considered adjunctive therapy, which could be tapered or stopped and restarted, as clinically required at the discretion of the investigator, during the study.

Rescue Therapies for AD

Use of TCS of high or super-high potency, topical phosphodiesterase type 4 (PDE4) inhibitors, oral or topical JAK inhibitors, phototherapy, **or systemic therapies for AD** during the 24-week treatment period will be considered use of rescue therapy in the analysis (Table 6-3). Allowed rescue therapies are those approved for treatment of AD as well as local standard of care. **Subjects may continue investigational product if there is concurrent use of topical rescue therapies (excluding topical**

JAK inhibitors), or phototherapy. Subjects may require temporary interruption of investigational product if systemic corticosteroids are used for ≤ 2 consecutive weeks to avoid concurrent administration with investigational product. Subjects must permanently discontinue investigational product if there is use of specific prohibited therapies: systemic corticosteroids for > 2 consecutive weeks, conventional non-biologic, non-targeted immunosuppressive systemic therapies, biologics, targeted systemic AD rescue therapies, or topical JAK inhibitors (see Table 6-2 and Table 6-3 for additional details).

Discontinuation of Study Treatment and Subject Discontinuation

Subjects who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures through week 24**,** which will correspond to their EOT visit, **including the vaccine administrations at week [redacted] and the vaccine response assessment at 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 who permanently discontinue investigational product and do not complete the remaining study visits through week 24 should complete the EOT visit at the next scheduled visit following the last dose of the investigational product.

Subjects who do not permanently discontinue investigational product through week 24 due to safety-related reasons or protocol-defined stopping rules will be eligible to enroll in the long-term maintenance study (Study [redacted]

Safety Follow-up

An SFU visit is required [redacted] after the last dose of investigational product for all subjects who do not enroll into the long-term maintenance study.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

A total of [redacted] subjects will be randomized in [redacted] ratio to rocatinlimab [redacted] mg (N = [redacted] and placebo (N = [redacted]). A maximum of up to [redacted] subjects will be included in in the [redacted]. [redacted]

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

4.2 Patient Input Into the Study Design

Patient input was not obtained for this study.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

This study will be used to investigate rocatinlimab [redacted] mg [redacted] for 24 weeks with an additional [redacted] mg dose on week [redacted]

In the phase 2 Study 4083-006, 3 dose levels and 2 dosing frequencies ([redacted] mg [redacted] mg [redacted] 300 mg Q2W, and [redacted] mg Q2W) were tested in subjects with moderate to severe AD. All doses were associated with improved IGA and EASI 75 responses compared with placebo. The adverse event profile was overall consistent across the different active treatment groups.

[redacted]

4.4 End of Study

The end of study (EOS) date for the entire study is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), including any additional parts in the study (eg, long-term follow-up, [redacted]), as applicable.

An individual subject is considered to have completed the study if they have completed the last visit shown in the Schedule of Activities (see Section 1.3). The total study duration for an individual subject is approximately [redacted] weeks.

5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening through the day 1 prerandomization visit.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

Both subjects naïve to meningococcal and/or tetanus vaccine and those who have received prior vaccine doses are eligible to participate in the study.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent/assent prior to initiation of any study specific activities/procedures.

102 Age 18 to 54 years.

103 Subject has a diagnosis of AD (according to American Academy of Dermatology Consensus Criteria [Eichenfield, 2014]) that has been present for at least **12** months before signing of informed consent.

104 Prior to informed consent, history of inadequate response **TCS** of medium or high **to higher potency (refer to Table 11-4)** [redacted]

105 vIGA-AD score ≥ 3 (on the 0 to 4 vIGA-AD scale, in which 3 is moderate and 4 is severe) at initial screening.

106 vIGA-AD score ≥ 3 (on the 0 to 4 vIGA-AD scale, in which 3 is moderate and 4 is severe) at day 1 prerandomization.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Other Medical Conditions

201 Active malignancy, multiple myeloma; myeloproliferative or lymphoproliferative disorder; or a history of any of these conditions within 5 years prior to informed consent (except curatively treated in situ cervical carcinoma, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma).

202 History of major immunologic reaction (eg, serum sickness, anaphylaxis, or anaphylactic reaction) to any other biologic product or any excipient of rocatinlimab.

203 History of Guillain-Barré syndrome (GBS).

204 Known sensitivity to any of the products or components to be administered during dosing.

205 Diagnosis of a helminth parasitic infection within 6 months prior to day 1 prerandomization that had not been treated with or had failed to respond to standard of care therapy.

206 Evidence of human immunodeficiency virus (HIV) infection or positive for HIV antibodies at initial screening or current acquired, common variable or inhibited, primary or secondary immunodeficiency.

207 Positive for hepatitis C virus (HCV) antibody at initial screening with confirmed positive HCV ribonucleic acid (RNA).

208 Active and non-virally suppressed hepatitis B infection at initial screening, defined as detectable hepatitis B deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) test in a subject with detectable hepatitis B surface antigen (HBsAg) and/or antibodies to hepatitis B core. Subjects with detectable HBsAg are required to be virally suppressed with an approved hepatitis B antiviral therapy during the study.

209 Positive or indeterminate QuantiFERON GOLD from central laboratory at initial screening

- Exception: A positive or indeterminate QuantiFERON test is allowed if ALL of the following are present at **Day 1 Prerandomization per Screening Tuberculosis (TB) Risk Assessment Questionnaire provided by Amgen**:
  - No symptoms of TB as per the worksheet provided by Amgen
  - Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB per local standard of care prior to start of investigational product)
  - No known exposure to a case of active TB after most recent prophylaxis
  - No evidence of active TB on chest radiograph obtained within 3 months prior to day 1 prerandomization

210 A corrected QT interval (QTc) of > 450 msec in males or > 470 msec in females at initial screening as assessed by the investigator, or history of long QT syndrome

211 Active chronic or acute infection requiring treatment with systemic antibiotics, antiviral, antiparasitic, antiprotozoal, or antifungals within 4 weeks before day 1 prerandomization.

212 Superficial skin infections within 2 weeks before day 1 prerandomization.

213 Severe depression, poorly controlled schizophrenia, or subjects who have had an inpatient psychiatric admission within the last year. Subjects who are receiving a psychiatric treatment regimen must be stable on treatment for at least 8 weeks prior to study day 1.

214 Any of the following laboratory abnormalities at screening:

- Estimated glomerular filtration rate < 30 mL/min/1.73 m^2
- Aspartate aminotransaminase (AST) or alanine aminotransaminase (ALT) ≥ 2.5 times the upper limit of normal (ULN)
- Neutrophil count < 1.5 x $10^3/\mu L$

[redacted]

Prior/Concomitant Therapy

217 Subjects for whom administration of the meningococcal vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine.

218 Subjects for whom administration of the tetanus, diphtheria, and pertussis vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine.

219 Subject is a recipient of any vaccine (except influenza virus vaccines or coronavirus disease 2019 [COVID-19] vaccines) within 3 months prior to screening, any meningococcal vaccine within 1 year prior to screening, or any tetanus-, diphtheria-, or pertussis-containing vaccine within 5 years prior to screening.

220 Treatment with any biologic immunosuppressive or immunomodulatory therapy for AD or any other autoimmune, inflammatory, or allergic diseases (eg, dupilumab, tralokinumab, lebrikizumab, other interleukin inhibitors, anti-immunoglobulin E [IgE], tumor necrosis factor [TNF] inhibitors) within 12 weeks or 5 half-lives, whichever is longer, prior to day 1 prerandomization.

221 Any cell depletion therapy within 12 months from initial screening or until cell count returns to normal before screening, whichever is longer.

222 Treatment with any of the following medications or therapies within 4 weeks or 5 half-lives, whichever is longer, prior to day 1 prerandomization:

- Systemic corticosteroids (inhaled corticosteroids, intra-articular steroid injection, eye, ear, or nasal drops containing corticosteroids are allowed, suppositories, or enemas containing corticosteroids are not allowed)
- Systemic treatment with methotrexate, mycophenolate, calcineurin inhibitors, or other immunosuppressants
- Phototherapy
- Oral or topical JAK inhibitors

223 Treatment with any of the following agents within 1 week before day 1 prerandomization:

- TCS **of any potency**
- TCI
- Topical PDE4
- Other topical immunosuppressive agents
- Combination topical agents containing a [redacted], PDE4 inhibitors, or other topical immunosuppressive agents

224 Treatment with live virus including live attenuated vaccination 12 weeks prior to day 1 prerandomization.

Prior/Concurrent Clinical Study Experience

225 Previous participation in a study including rocatinlimab (formerly AMG 451 and KHK4083) or any therapy selectively targeting OX40/OX40L and receipt of active investigational product.

226 Currently receiving treatment in another investigational device or drug study, or less than 30 days (16 weeks for Japan) since ending treatment on another investigational device or drug study(ies) **prior to day 1 prerandomization**. Other investigational procedures while participating in this study are excluded.

Other Exclusions

227 Female subjects of childbearing potential unwilling to use protocol-specified method of contraception see Appendix 5 (Section 11.5) during treatment and for an additional 16 weeks after the last dose of investigational product.

228 Female subjects who are breastfeeding or who plan to breastfeed while on study through 16 weeks after the last dose of investigational product.

229 Female subjects planning to become pregnant while on study through 16 weeks after the last dose of investigational product.

230 Female subjects of childbearing potential with a positive pregnancy test assessed at initial screening and day 1 prerandomization by a highly sensitive serum or urine pregnancy test, respectively.

231 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments **[COAs]**) to the best of the subject and investigator's knowledge.

232 History or evidence of any other clinically significant disorder (including concomitant dermatologic conditions such as psoriasis) or disease, including non-AD dermatologic conditions (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety, or interfere with the study evaluation, procedures or completion.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

The pathogenesis of AD associated with food allergy is complex. The importance of diet as a potential trigger of AD has been a subject of debate for a long time (Lever, 2001). However, there is not enough evidence that can demonstrate improvement in AD through dietary elimination, so this is not recommended routinely. Study subjects should be encouraged to adhere to their usual diet and avoid any foods known to trigger allergic sensitivity of their AD for the duration of the study.

5.3.2 Activity

Emotional stress, defined as general response of the body to external or internal challenges to the AD pathology, can impact disease severity. Factors like lifestyle and leisure activities may change the behavior of immune cells in AD with an impact on the evolution of the disease (Bridgette and Noren, 2017). However, there is not enough evidence that can demonstrate improvement in AD through specific activity elimination, so this is not recommended routinely. Study subjects should be encouraged to adhere to usual activity and avoid any activities known to affect their AD.

5.4 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or the subject's legally authorized representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

Each subject who enters into the screening period for the study ((defined as when they sign the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned via IRT. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

Subjects are eligible to be enrolled in the study when the investigator **determines** that the subject has met all eligibility criteria. Subjects are considered enrolled at the time when a randomization number is assigned via IRT. The investigator is to document enrollment decision and date, in the subject's medical record and in/on the Subject Enrollment Case Report Form (CRF) via IRT.

Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure), regardless of reason, may be rescreened 1 time. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), [redacted], or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that according to local regulations in several countries, investigational product(s) described in Section 6.1.1 are referred to as investigational medicinal product(s) and [redacted]

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

6.1.1.1 Rocatinlimab

Table 6-1. Investigational Products

Study Treatment Name	Amgen Investigational Product:[a] Rocatinlimab	Placebo
Dosage Formulation	[redacted] mg/mL Supplied as a single-use, preservative free solution for injection	Placebo will be presented in identical containers, and stored/packaged the same as rocatinlimab
Unit Dose Strength(s)	[redacted] mg per vial	N/A
Dosage Level(s)	Rocatinlimab [redacted] mg [redacted] with a loading dose given at week [redacted]	Placebo [redacted] with a loading dose given at week [redacted]
Route of Administration	SC injection	
Accountability	The quantity of investigational product administered per vial, start date/time, and box number of investigational product are to be recorded on each subject's CRF(s).	
[redacted]		
Dosage Preparation	Information regarding dose preparation/administration will be provided to the site.	

CRF = case report form; N/A = not applicable; SC = subcutaneous; [redacted].
[a] Rocatinlimab/placebo will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.1.2 Tetanus and Meningococcal Vaccines

The vaccines are not investigational products, but they are being studied for the potential effect on the investigational product. At the week [redacted] visit, subjects will each receive 1 dose of tetanus (**for example** TENIVAC®, TDVAX®, Adacel®, or Boostrix®) and 1 dose of meningococcal (**for example** Menactra®, Menveo®, or MenQuadfi®) vaccines at time points according to the Schedule of Activities (see Section 1.3). The blood samples for tetanus IgG antibody level and meningococcal IgG antibody level will be collected and vaccines will be administered by trial staff on the same day the investigational product injection is administered; the blood samples will be taken first, then vaccines will be given, and then the investigational product will be given. The 2 vaccines will be given intramuscularly in the deltoid muscle of the upper arms, 1 vaccine in each arm. The injection site must be recorded in the source documents and recorded on the Case Report Form (CRF). The subject will be kept under observation for 30 minutes following vaccination. After this observational period, the investigational product injection will be given (refer to Table 6-1). Note that at week [redacted] the investigational product injection will be given in the upper thigh or abdomen.

Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat acute anaphylactic reactions must be immediately available at trial sites, and trial personnel should be trained to recognize and respond to anaphylaxis according to local guidelines.

6.1.2 Non-investigational Products

There are no non-investigational products in this study.

6.1.3 Medical Devices

Investigational medical devices will not be used in this study.

In a substudy, a wrist-worn activity monitoring device will be used according to its intended use, to capture sleep and daily physical activity. Subjects in this **sub**study will be asked to wear an activity monitor to measure their activity and sleep. The activity monitor generates data that is then captured by a mobile application on the study provided mobile device. Subjects will be instructed to wear the activity monitor on their non-dominant wrist and use the mobile device to upload the activity monitor data at home until the deployment period is completed.

The activity monitor captures high-resolution movement data during the study. Activity monitor data is uploaded via internet to a secure database. An upload every hour will

occur automatically via wireless Bluetooth® when the activity monitor comes in proximity to the mobile device. Any adverse events associated with the [redacted] will be captured in the Events CRF as a procedure related event.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices. [redacted]

6.1.4 Other Protocol-required Therapies

All other protocol-required therapies including emollients, that are commercially available, may be reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Study-required vaccines (tetanus and meningococcal vaccines) will be reimbursed by Amgen if not covered under standard of care (SOC) or insurance. The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Vaccine administration will be done at the week [redacted] visit of the study.

6.1.5 Other Intervention Procedures

There are no other interventional procedures in this study.

6.1.6 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational products provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with an investigational product supplied by Amgen are to be reported.

6.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

6.1.7.1 Atopic Dermatitis Rescue Therapy

Topical and systemic rescue therapies for AD are **discouraged** during the **study period with the investigational product** (see Section 6.8.3).

6.1.7.2 Other Excluded Therapies for Atopic Dermatitis or Related Conditions

The use of the following therapies is prohibited at any time during the study. Subjects may continue investigational product if there is concurrent use of any of these therapies:

Emollients containing added pharmacological agents with antipruritic, antiseptic, and/or keratolytic properties, such as urea ≥ 20%, ammonium lactate ≥ 12%, or salicylic acid ≥ 3%

Antihistamines for treatment of pruritus

6.1.7.3 Guidance for Certain Therapeutics for Non-atopic Dermatitis Related Conditions, Including Prohibited Therapies

Guidance for therapeutics for non-AD related conditions is provided in Table 6-2.

Table 6-2. Guidance for Certain Therapeutics for Non-atopic Dermatitis-related Conditions, Including Prohibited Therapies

Therapies if given for non-AD-related conditions	**Restrictions**	**Requires Permanent Investigational Product Discontinuation**
• Live vaccines • Any investigational product in another device or drug study	Always prohibited	**Permanent discontinuation**
• Systemic corticosteroids (**eg,** oral, IV, **or** intramuscular)	Strong recommendation to use alternative non-systemic therapy for non-AD-related indications prior to using systemic therapies	**If treatment duration ≤ 2 consecutive weeks** • **May require t**emporary interruption **to avoid concurrent administration** • **No temporary interruption required if systemic corticosteroid and adequate washout period (5 half-lives) are completed by next investigational product dose** **If treatment duration > 2 consecutive weeks** • **Permanent discontinuation**

• **Conventional immunosuppressive or immunomodulatory agents (non-biologic, non-targeted), eg,**
  • **Cyclosporine**
  • **Azathioprine**
  • **Methotrexate**
  • **Mycophenolate**
	Strong recommendation to use alternative non-systemic therapy for non-AD-related indications prior to using systemic therapies	**Permanent discontinuation**

Page 1 of 2

Footnotes defined on last page of this table.

Table 6-2. Guidance for Certain Therapeutics for Non-atopic Dermatitis Related Conditions, Including Prohibited Therapies

Therapies if given for non-AD-related conditions	Restrictions	Requires Permanent Investigational Product Discontinuation
• Immunosuppressive or immunomodulatory biologics for the treatment of non-AD autoimmune, inflammatory, or allergic diseases (eg, dupilumab, interleukin inhibitors, anti-IgE, **or** TNF inhibitors) • Immunotherapy (eg, PD1 inhibitors), cytotoxic, or cell-depleting therapies (eg, cyclophosphamide) • Oral kinase inhibitors (eg, inhibitors of JAK, BTK, or TYK2)	Prohibited until 16 weeks after discontinuation of investigational product	**Permanent discontinuation**

Page 2 of 2

AD = atopic dermatitis; BTK = Bruton's tyrosine kinase; IgE = immunoglobulin E; IV = intravenous; JAK = Janus kinase; PD1 = programmed cell death 1 receptor; TNF = tumor necrosis factor TYK2 = tyrosine kinase 2.

6.2 Dose Modification

6.2.1 Dose-group Study Escalation/De-escalation and Stopping Rules

Not applicable.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.2.2.1 Amgen Investigational Product: Rocatinlimab/Placebo

The following **adverse** events require permanent discontinuation from investigational product:

- Anaphylactic reaction or other serious hypersensitivity/allergic reaction assessed as related to investigational product by the investigator
- Malignancy (excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin)
- Opportunistic infection, such as active TB and other infections whose nature or course may suggest an immunocompromised status
- Serious or severe infection requiring systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents for longer than 2 weeks

[redacted]

The investigator should immediately refer the subject for mental health assessment and treatment, as per local standard of care (see Sections [redacted] and 8.2.8)

- Severe depression **and subjects with significant worsening of depression** as assessed by the investigator. The investigator should immediately refer the subject for mental health assessment and treatment, as per local standard of care (see Sections 8.2.7 and 8.2.8)
- Other serious neuropsychiatric event requiring psychiatric hospitalization
- Any of the following laboratory results:
  - Neutrophil count ≤ **0.5** x 10^9/L **confirmed by 2 consecutive tests (confirmatory test by the central laboratory must be performed as soon as possible, and results reviewed prior to next scheduled dose).**
  - Hepatotoxicity meeting criteria for permanent discontinuation of investigational product as provided in Table 11-3.

The following adverse events require temporary interruption of investigational product:

- **Presence of a serious or severe infection on the day of a scheduled investigational product. Investigational product may resume at the discretion of the principal investigator (PI) or in consultation with the medical monitor.**

Use of certain rescue therapies may require permanent discontinuation or temporary interruption of investigational product (see Table 6-2 and Table 6-3).

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on drug accountability for the investigational product will be provided to the site.

If permitted by local regulations, the site may ship investigational product to the subject. If the site does not have its own courier, shipment can be organized by a third-party courier engaged by sponsor. The courier's information must be included on the Delegation of Authority Form. The investigator is responsible for directing and supervising the shipment and activities of the courier. Subjects should be informed of their responsibilities for

receipt, handling, storage, and accountability if site to patient shipments will be performed. Additional guidance will be provided to the site. There is no additional risk to subjects with the Site to Patient process. Site to Patient specific training will be provided and support materials for the sites and subjects as necessary. Management of temperature data and status check of investigational product will be completed post-delivery by way of courier review of the temperature logger.

6.4 Method of Treatment Assignment

The randomization for the treatment period as described in Section 4.1 will be performed by IRT. The randomization date will be captured in IRT.

6.5 Blinding

This is a double-blind study. Unblinding information consists of subject treatment assignments, including contents of investigational product boxes (eg, manufacturing lot number), and potentially unblinding data which has the potential to indicate treatment assignment for an individual subject.

The following assessments will also be considered unblinding information:

Unblinding information will be blinded to all subjects, site personnel, and Amgen study personnel or designees as described below (see Sections 6.5.1.1 and 6.5.1.2).

6.5.1.1 Site Personnel Access to Unblinding Information

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified immediately and no later than 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

Except for emergency unblinding of individual subjects, unblinding information will not be accessible by investigative sites or subjects prior to **all subjects receiving blinded**

maintenance treatment in the **long-term maintenance study (Study** [redacted] **having switched to open-label treatment** of **completed** the **SFU**.

6.5.1.2 Access to Unblinding Information by Amgen or Designees

Preidentified members of the clinical study team will be unblinded in order to conduct the primary analysis (see Section 9.4.1.2). To ensure trial integrity, the unblinded members will not be involved in study conduct activities for the remainder of the study. Other members of the study team will not have access to unblinding information **prior to all subjects receiving blinded maintenance treatment in** the **long-term maintenance study (Study** [redacted] **having switched to open-label treatment** o**r completed** the **SFU**.

6.6 Treatment Compliance

When subjects are dosed at the site, they will receive rocatinlimab or placebo directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the CRF.

6.7 Treatment of Overdose

Overdose, defined for the purpose of this study as any dose above the highest dose specified in this protocol (see Section 6.1), is anticipated to be low. The investigational product will be administered under medical supervision by qualified personnel and the maximum possible dose to be administered in case of dosing preparation error is [redacted] mg. Treatment of overdose of rocatinlimab consists of general supportive measures directed to the observed clinical effects. There is no known specific antidote for overdose of rocatinlimab. In the event of an overdose, the investigator should:

- Contact the Amgen medical monitor immediately.
- Closely monitor the participant for any adverse event/serious adverse event and laboratory abnormalities for at least 16 weeks after the administration of the suspected overdose.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8 Prior and Concomitant Treatment

6.8.1 Prior Treatment

[redacted]

6.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care in accordance with the restrictions listed in Section 6.1.7. Subjects will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study.

The following non-exhaustive list of therapies is permitted during the study and will not be considered as rescue therapies:

- For those subjects on stable dosing of prescription sleep medications at entry, downward dose adjustments or discontinuation of treatment may occur during the study.
- Non-sedating antihistamines including, but not limited to, acrivastine, bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, mizolastine, and rupatadine are allowed for treatment of allergic conditions other than AD. Use of antihistamines for treatment of pruritus is **discouraged** during the study.
- Single intra-articular or soft tissue (bursa, tendons, and ligaments) corticosteroid injection is allowed.

- Intranasal or inhaled steroid use is allowed.
- Topical anesthetics and topical and systemic anti-infective medications are allowed.
- Ophthalmic drugs containing antihistamines, corticosteroids or other immunosuppressants are allowed.
- Treatment with concomitant therapies for other medical conditions such as diabetes, hypertension, hyperlipidemia, and psychiatric illnesses is permitted during the study.

Concomitant therapies are to be collected from enrollment through the **EOS**. All concomitant medications or treatments, whether prescription or over the counter, during the course of the study, must be recorded on the concomitant medication electronic Case Report Form (eCRF). Any changes must be recorded.

For concomitant therapies being taken, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.8.3 Rescue Therapies for Atopic Dermatitis or Related Conditions

In the event of worsening and/or unacceptable symptoms of AD despite at least 6 weeks of treatment with investigational product and twice-daily use of emollients, rescue with standard of care therapies may be given if deemed necessary by the investigator. Rescue therapies for AD are defined as therapies concordant with AD treatment and are listed in Table 6-3. It is recommended to use topical rescue therapies before considering using systemic rescue.

Any use of rescue therapy as described in Table 6-3 will result in the subject being considered a nonresponder for all subsequent efficacy assessments in the analysis (Section 9.4.2.2).

Table 6-3. Rescue Therapy for Atopic Dermatitis

Rescue Therapy for AD	If deemed necessary, when permitted for use	Requires Permanent Investigational Product Discontinuation
Topical rescue therapy and phototherapy: • **Topical corticosteroids of high and super-high potency[a]** • **Topical PDE4 inhibitors** • **Other topical immunosuppressive agents with the exception of topical JAK inhibitors (see below)**	**Use is discouraged during study, however permitted if deemed necessary.**	**No**

Rescue Therapy for AD	If deemed necessary, when permitted for use	Requires Permanent Investigational Product Discontinuation
• Any combination therapy with TCS of high and super-high potency, PDE4 inhibitors, or other topical immunosuppressive agents • Phototherapy		
Systemic corticosteroids (eg, oral, intravenous, or intramuscular)	Use is discouraged during study, however permitted if deemed necessary. Note: Recommend consideration of topical rescue therapies first	If rescue treatment duration ≤ 2 consecutive weeks: • May require temporary Interruption to avoid concurrent administration • No temporary interruption required if rescue treatment and an adequate washout period (5 half-lives) have completed by next investigational product dose If rescue treatment duration > 2 consecutive weeks: • Permanent discontinuation
Conventional immunosuppressive systemic therapies (nonbiologic, nontargeted), eg, • Cyclosporine • Azathioprine • Methotrexate • Mycophenolate	Use is discouraged during study, however permitted if deemed necessary. Note: Recommend use of topical rescue therapies before escalating to systemic rescue therapy	Permanent discontinuation
Biologic or targeted systemic AD therapies, including: • Biologics (eg, dupilumab, tralokinumab)	At least 16 weeks after discontinuation of the investigational product Note: Recommend use of topical rescue therapies	Permanent discontinuation

Rescue Therapy for AD	If deemed necessary, when permitted for use	Requires Permanent Investigational Product Discontinuation
• **Oral JAK inhibitors (eg, upadacitinib, baricitinib, abrocitinib)** • **Topical JAK inhibitors (eg, ruxolitinib cream)**	**before escalating to systemic rescue therapy**	

AD = atopic dermatitis; JAK = Janus kinase; PDE4 = phosphodiesterase 4 inhibitor; TCS = topical corticosteroids.
[a] A full list of topical corticosteroids and potency category is provided in Appendix 8 (Section 11.8).

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative) can decline to continue receiving investigational product and/or other protocol-required therapies and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and product complaints (including device-related adverse events, as applicable) and must document this decision in the subject's medical records. **Subjects are encouraged to complete all remaining study visits and procedures, including the vaccine administrations at week [redacted] and the vaccine response assessment at week 24, with the exception of investigational product administration and post-dose monitoring procedures through week 24 after permanent discontinuation of investigational product.** Subjects who have discontinued investigational product

and/or other protocol-required therapies and/or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments may include any of the following:

- decision by sponsor
- lost to follow-up
- death
- adverse event
- subject request
- ineligibility determined
- protocol deviation
- non-compliance
- requirement for alternative therapy **(see Table 6-2 and Table 6-3)**
- pregnancy

7.2 Subject Discontinuation/Withdrawal From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

If a subject withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death

- lost to follow-up

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator should search publicly available records, where permitted, to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Section 1.3).

If an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (see Section 1.3), is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is **a minimum of** [redacted] **days (inclusive) and** up to [redacted] days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.5) as applicable.

If a subject has not met all eligibility criteria at both initial screening and day 1 prerandomization visits, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1 time.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than [redacted] days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 1.3). On-study visits may be completed within ± 3 days. The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-required therapies is to be administered last during each visit that it is required.

8.1.3 End of Treatment

Subjects who permanently discontinue investigational product for any reason before week 24 are encouraged to complete all remaining study visits and procedures, **including the vaccine administrations at week [redacted] and the vaccine response assessment at 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 who permanently discontinue investigational product and do not complete the remaining study visits through week 24 should complete the EOT visit at the next scheduled visit following the last dose of investigational product (see W24/EOT in Section 1.3).

8.1.4 Safety Follow-up

An SFU visit is required [redacted] after the last dose of investigational product for all subjects who do not continue into the long-term maintenance study (Study [redacted]

An additional SFU visit will not be required for subjects who discontinue investigational product and do not enroll into the maintenance study but who complete the remaining study visits for at least [redacted] after the last dose of investigational product before or at week 2**4**.

8.1.5 End of Study

Refer to Section 4.4 for the **EOS** definition.

All end of study procedures should be performed at the final visit for subjects who discontinue study before the defined end of study visit.

8.2 General Assessments

8.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed **(see Section 12.3 [Appendix 3] for further details).**

If remote consent is used:

1. The subject should be sent a blank informed consent form/informed consent addendum via mail or email.
2. A member of the study site team (investigator or designee) will call the subject to walk through the document via phone and answer questions. The time and date of the phone conversation should be recorded in the subject's medical record.
3. The subject should sign the informed consent form/informed consent addendum after all questions are answered and return the original or scanned copy via mail or email, respectively. The date and time of the subject's consent should be recorded in the medical record. The subject should take a photograph of the signature page and send it to the person conducting the informed consent discussion.
4. The person who conducted the informed consent discussion should then sign and date the informed consent form/informed consent addendum, when received.
5. A fully signed version of the informed consent form/informed consent addendum should be provided to the subject.

8.2.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on [redacted] of the protocol-required therapies.

8.2.3 Medical History

The Investigator or designee will collect a complete medical, dermatological, immunological, and surgical history. Medical history will include information on the

subject's concurrent medical conditions. The current severity will be collected for each condition that has not resolved. Record all findings on the medical history CRF. The investigator or designee will also collect any cardiovascular history and cardiovascular risk factors.

In addition to the medical history above, AD history must date back to the original diagnosis.

8.2.4 Physical Examination

A complete physical examination will be **conducted at screening and cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. At subsequent study visits, a symptom-directed physical examination may be conducted at the discretion of the investigator** per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, **m**edical **h**istory, event**s**).

8.2.5 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

8.2.6 Substance Use History

Obtain a detailed history of prior and/or concurrent use of alcohol, recreational drugs, and tobacco.

[redacted]

8.2.8 Mental Health Assessment

As AD is associated with high rates of depression and [redacted] **compared to the general population, screening and on-study monitoring of mental health will be performed. Central Mental Health professionals contributing to this study will have adequate training to assess psychiatric conditions in the study population**.

[redacted]

Screening

Investigators must review relevant data at screening, including but not limited to, medical history, **prior and current medications, substance use,** [redacted]

[redacted]

The investigator should immediately refer the subject to local mental health assessment and treatment as per **local** standard of care. Subjects ineligible due to depression [redacted] or behavior may be rescreened once after **1 year or** 6 months **respectively**.

On-Study

Subjects with severe depression as **assessed** by the investigator, are to **permanently** discontinue investigational product and should immediately be referred to mental health assessment and treatment, as per local standard of care.

Any psychiatric adverse event is to be followed and reported in the Events CRF as provided in Section 8.5.6. Referral to mental health services must be entered by the investigator in the Other Action Taken field of the corresponding adverse event.

8.3 Assessment of Vaccine Responses

Blood samples for assessment of vaccine-specific serum antibody responses will be collected at the time points specified in the Schedule of Activities (see Section 1.3).

The antibody response to tetanus vaccine will be assessed by measuring serum anti-tetanus immunoglobulin G (IgG) by an immunoassay. The antibody response to meningococcal vaccine will be assessed by measuring serum anti-meningococcal IgG by an immunoassay.

Reporting in eCRF

It will be recorded in the eCRF if the blood samples to assess vaccine response were taken; if not, a reason will be provided.

8.4 Efficacy Assessments

Clinical evaluations of AD should be performed by an experienced and qualified dermatologist (board certified or equivalent). An experienced and qualified non-dermatologist physician or experienced medical professional with experience in the conduct of AD clinical trials may be permitted to perform the clinical evaluations of AD when designated by the primary site Investigator. The evaluator must receive and document protocol-specific and applicable efficacy assessment scales training prior to performing these evaluations. To assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual subject throughout the study whenever possible; a back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation. **At each visit, COAs are to be performed prior to any other activity specified in the Schedule of Activities (see Section 1.3).**

8.4.1 Assessments Completed by Investigator

Efficacy assessments should be collected on an electronic **device** and completed at scheduled visits.

8.4.1.1 Validated Investigator Global Assessment for Atopic Dermatitis

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 (clear) to 4 (severe) (Simpson et al, 2020) (Copyright © 2017 Eli Lilly and Company – used with the permission of the Eli Lilly and Company under a Creative Commons Attributable-No Derivatives 4.0 International License - https://creativecommons.org/licenses/by-nd/4.0/). The vIGA-AD score will be assessed at time points according to the Schedule of Activities (see Section 1.3). To enable the harmonization of clinical efficacy results of

this investigational AD drug, the vIGA-AD and associated training module available through the International Eczema Council will be used in this protocol.

The vIGA-AD is provided in the study reference manual and will be assessed at the time points shown in the Schedule of Activities (see Section 1.3). Whenever possible, the vIGA-AD should be assessed by the same investigator at each visit to reduce the inter-rater variability.

[redacted]

8.4.1.3 Eczema Area and Severity Index

The EASI was designed by modifying the Psoriasis Area and Severity index, which has been widely used in clinical trials and has been established as a well-accepted and standardized instrument for assessing therapeutic response in patients with psoriasis (Schmitt et al, 2007). The EASI evaluates 4 natural anatomical regions for severity and extent of key disease signs and focuses on key acute and chronic signs of inflammation (ie, erythema, induration, papulation, excoriation, and lichenification). The maximum score is 72, with higher values indicating more severe disease.

The EASI will be assessed at the time points shown in the Schedule of Activities (Section 1.3). Whenever possible, the EASI should be assessed by the same investigator at each visit to reduce the inter-rater variability.

[redacted]

8.4.1.5 Severity Scoring of Atopic Dermatitis

The severity scoring of atopic dermatitis (SCORAD) is a measurement tool for assessing the severity (ie, extent, intensity) of AD using both physician and patient-reported data.

The tool evaluates the extent and intensity of the AD lesions, along with subjective symptoms (Kunz et al, 1997). The SCORAD will be assessed at the time points shown in the Schedule of Activities (Section 1.3). The SCORAD should be assessed by the same investigator at each visit, whenever possible, to reduce inter-rater variability. The patient-reported items of the SCORAD will be assessed at the study center at the time points indicated in the Schedule of Activities (Section 1.3). **Severity scoring of atopic dermatitis will only be assessed among subjects who participate the [redacted].**

8.4.2 Assessments Completed by Subject

8.4.2.1 Hospital Anxiety and Depression Scale

The HADS is a self-assessment questionnaire that has been found to be a reliable instrument for detecting states of anxiety and depression in the setting of hospital outpatient clinic. The HADS questionnaire has 7 items each for depression and anxiety subscales. The HADS will be assessed at the study center at the time points indicated in the Schedule of Activities (Section 1.3). **Table 8-1 includes HADS Anxiety and Depression Score Categorization Scores. These categorizations are listed to support the investigator's screening of a subject's level of anxiety and depression, however** diagnosis of **depression and assessment of the severity of depression should be made by a qualified clinician.**

Table 8-1. Hospital Anxiety and Depression Score Categorization

HADS-depression or HADS-anxiety Score	Categorization
0 to 7	Normal
8 to 10	Mild
11 to 14	Moderate
15 to 21	Severe

HADS = Hospital Anxiety And Depression Scale

8.4.2.2 Worst Pruritus NRS

In the electronic daily diary assessment, subjects report the severity of pruritus over the past 24 hours. The Worst Pruritus is an NRS comprised of 1 item and represents the numbers 0 to 10. Subjects are asked to rate the intensity of their worst itch using this scale with 10 being the highest amount of itch. It features high reliability and concurrent validity and is an appropriate choice for all subjects due to its simple format. At initial screening, subjects are asked to rate the intensity of their worst pruritus using this NRS with a 7-day recall. **Worst Pruritus NRS will only be assessed among subjects who participate the [redacted].**

8.4.2.3 Atopic Dermatitis Skin Pain NRS

In the electronic daily diary assessment, subjects report the severity of AD skin pain over the past 24 hours. The AD Skin Pain is an NRS comprised of 1 item and represents the numbers 0 to 10. Subjects are asked to rate the intensity of their AD skin pain using this scale with 10 being the highest amount of AD skin pain. **Atopic Dermatitis skin pain will only be assessed among subjects who participate the** [redacted]

8.4.2.4 Sleep Disturbance NRS

In the electronic daily diary assessment, subjects report the quality of their sleep over the past 24 hours. The Sleep Disturbance is an NRS comprised of 1 item and represents the numbers 0 to 10, with 10 being the highest amount of sleep disturbance. Subjects are asked to rate the intensity of their sleep disturbance using this scale. Content validity is established and is an appropriate choice for all subjects due to its simple format. **Sleep disturbance NRS will only be assessed among subjects who participate the** [redacted]**.**

8.4.2.5 Sleep Assessments

Consensus Sleep Diary-Atopic Dermatitis (CSD-AD) will be used to report sleep patterns via the daily e-Diary among subjects who participate the [redacted] **Sleep-related parameters include following:**

8.4.2.5.1 Sleep Onset Latency (SOL)

Sleep onset latency (SOL; in minutes) **will be collected by asking subjects how long it took** to fall **a**sleep **during the previous night**.

8.4.2.5.2 Wakefulness After Sleep Onset (WASO)

The wakefulness after sleep onset (WASO) is calculated as the time awake (in minutes) after initial sleep onset but before the final awakening for the day. Data for WASO will be collected by asking **subjects** how much time they were awake in total during the previous night.

8.4.2.5.3 Total Sleep Time (TST)

The total sleep time (TST) in minutes is calculated as the time of waking up for the day - the time of falling sleep – WASO **during the previous night**.

8.4.2.5.4 Sleep Efficiency

Sleep efficiency **during the previous night** is calculated as the (TST/[Time of waking up for the day - Time of trying to fall sleep]) x 100%.

8.4.2.6 Patient Oriented Eczema Measure (POEM)

The POEM is a 7-item validated questionnaire used to assess disease symptoms in children and adults (Charman, 2004). It evaluates time spent in the past week with AD signs and symptoms: individual items of bleeding, oozing, cracked, flaking and dry/rough skin, and their impact on sleep. The POEM will be assessed at the study center at the time points indicated in the Schedule of Activities (Section 1.3) **among subjects who participate the** [redacted].

8.4.2.7 Patient Global Impression of Severity (PGI-S)

The PGI-S is a single item designed to capture the subject's perception of symptom severity at the time of completion on a categorical response scale. There will be 2 PGI-S items, 1 each for AD skin pain and sleep disturbance. The PGI-S will be completed by the subject at the study center according to the Schedule of Activities (Section 1.3) **among subjects who participate the** [redacted].

8.4.2.8 Patient Global Impression of Change (PGI-C)

The PGI-C is a single item designed to capture the subject's perception of response to treatment at the time of completion. The assessment uses a 7-point rating scale, very much better to very much worse. There will be 2 PGI-C items, one each for AD skin pain and sleep disturbance. The PGI-C will be completed by the subject at the study center according to the Schedule of Activities (Section 1.3) **among subjects who participate the** [redacted].

8.5 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Section 1.3).

8.5.1 Vital Signs

The following measurements must be performed before administration of investigational product as specified in the Schedule of Activities (Section 1.3): systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a rested and calm state for at least 5 minutes before blood pressure assessment is conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

8.5.2 Post-dose Monitoring and Vital Signs

Subjects **must** be **monitored** for 2 hours following **at least** the first **2 doses** of investigational product **at** day 1 and **week** [redacted] **treatment period. If no systemic injection-related reactions, including immediate type hypersensitivity reactions, are observed after the first 2 doses, the post-dose monitoring period may be reduced to at least 30** minutes **for** subsequent **open-label** doses**. If systemic injection-related reactions are observed after the first 2 doses, the 2-hour post-dose monitoring period will remain as needed**. Any subject experiencing an acute reaction must receive immediate medical assessment and indicated supportive management according to the institutional standard of care and investigator judgement until the signs/symptoms of the reaction have resolved.

Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature must be measured at the end of the post-dose monitoring period before the subject is discharged at specific time points described in the Schedule of Activities (Section 1.3) and Section 8.4.1. Record all measurements on the vital signs CRF.

Clinically significant changes in vital signs as assessed by the investigator and any adverse events are to be reported as per Section 8.5.6.

8.5.3 Electrocardiograms

Subject must be in supine position in a rested and calm state for at least 5 minutes before electrocardiogram (ECG) assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The screening ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals. The **PI**, or designated site physician, will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Findings should be recorded on the ECG eCRF and any adverse event is to be recorded as per Section 8.5.6.

8.5.4 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Events CRF. The investigator must determine whether an abnormal value in an individual study subject

represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

Laboratory results that could potentially unblind the individual treatment assignment (see potentially unblinding laboratory analytes in Appendix 2 [Section 11.2]) will not be reported to investigative sites or accessible by blinded personnel **prior to all subjects receiving blinded maintenance treatment in the long-term maintenance study (Study [redacted] having switched to open-label treatment or completed the SFU**.

8.5.5 Other Safety

Not applicable for this study.

8.5.6 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.5.6.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.5.6.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Severity Intensity Scale for Adverse Events and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the W24/EOT visit for subjects who enroll in the long-term maintenance study (Study [redacted] and through the **SFU** visit for subjects who do not enroll in the long-term maintenance study, are reported using the Events CRF.

Adverse events of special interest (AESIs) including but not exclusive to infections, injection related reactions, hypersensitivity reactions, major adverse cardiovascular events (MACE), malignancy, neuropsychiatric adverse events,

aphthous ulcer, conjunctivitis, and gastrointestinal ulceration/perforation will be monitored.

8.5.6.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the W24/EOT visit for subjects who enroll in the long-term maintenance study (Study [redacted] and through the safety follow-up visit for subjects who do not enroll in the long-term maintenance study, are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee immediately and no later than 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor immediately and no later than 24 hours of it being available.

8.5.6.1.3 Adverse Event Adjudication

Potential Cardiovascular Events

In order to evaluate cardiovascular events in adult subjects during the study, all deaths, and the following serious cardiovascular (CV) events, that are deemed to be of potential cardiovascular origin or etiology, will be submitted to an independent committee for adjudication. Serious adverse events with terms mapping to a predefined preferred term list potentially indicative of cardiovascular etiology will also be adjudicated. All serious adverse events will be collected, recorded, and reported to the sponsor or designee immediately and no later than 24 hours of the investigator's awareness of the event, as indicated in Section 11.4.

8.5.6.1.4 Serious Adverse Events After the Protocol Required Reporting Period

There is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event.

Serious adverse events reported after the end of the study will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

8.5.6.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to inquire introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to about adverse event occurrence. If a subject reports or the investigator observes an adverse event of reaction at the site of study drug administration, the investigator is to capture as part of the primary event verbatim in the Events CRF the location of the reaction together with the type of reaction that better describes the event(s) (eg, injection site pain, injection site erythema, injection site induration, injection site swelling, injection site itching) with clear start and stop dates, rather than only using a general term of "injection site reaction." If there are multiple signs or symptoms at an injection site, each symptom of the event should be reported individually.

8.5.6.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen immediately and no later than 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

8.5.6.4 Regulatory Reporting Requirements for Safety Information

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

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

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For studies in which the treatment assignment is blinded, to comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report [ASR] in the European Union) for the Amgen Investigational Product. In order to ensure that consolidated safety information for the trial is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical trial, if applicable.

8.5.6.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.5.6.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects will be collected after the start of study treatment and until 16 weeks after the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

Pregnancy Testing

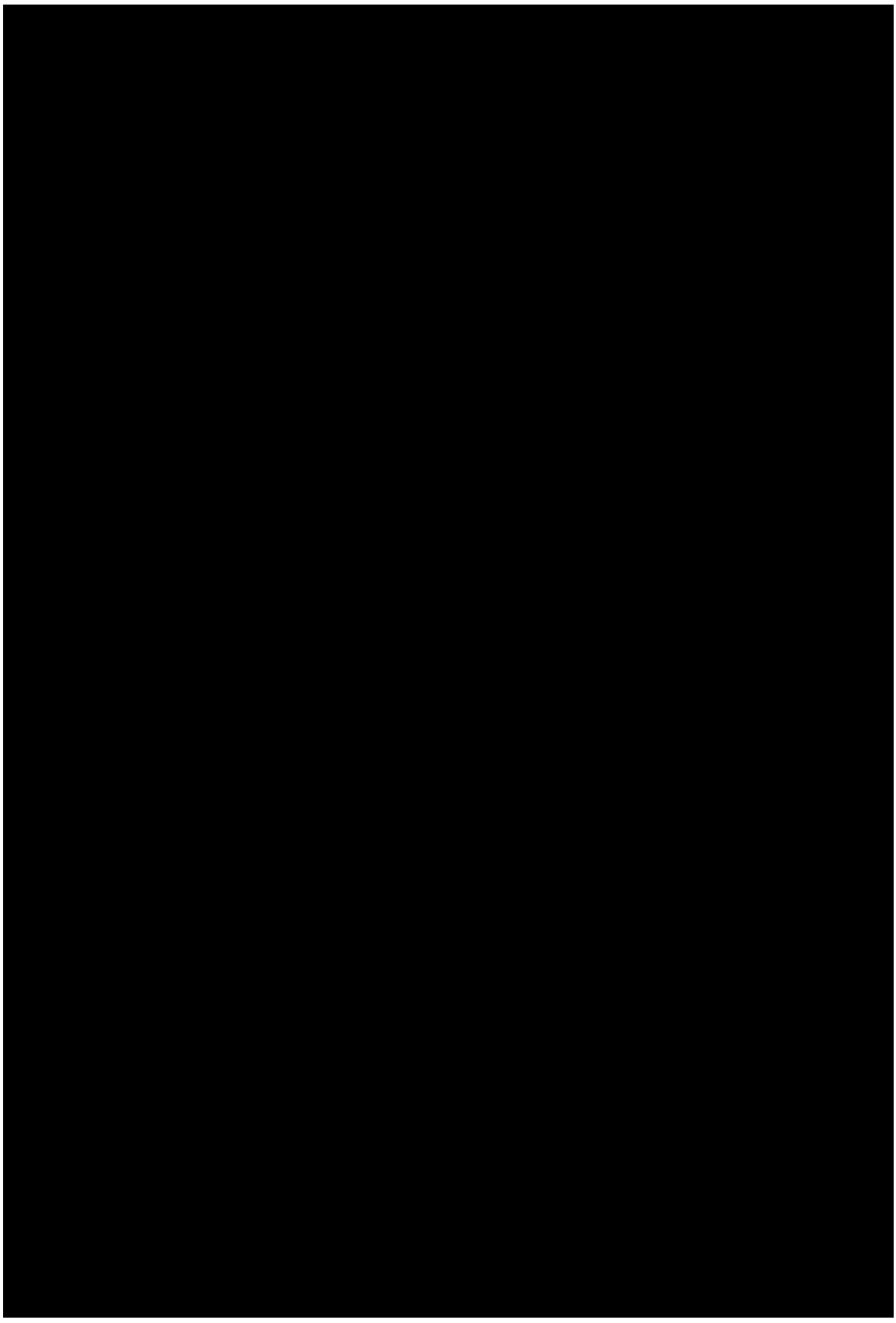
A highly sensitive serum pregnancy test should be completed at initial screening and a confirmatory urine pregnancy test should be completed on day 1 prerandomization for childbearing age females, as described in the Schedule of Activities (see Section 1.3).

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-3.) Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing should be performed [redacted] during treatment with protocol-required therapies and at the SFU visit when applicable, or 16 weeks after the last dose of investigational product for subjects who discontinue treatment prematurely.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

[redacted]



8.10 Other Assessments

8.10.1 Tuberculosis Testing and Tuberculosis Risk Assessment Questionnaire

Screening

All subjects must receive QuantiFERON GOLD test from central laboratory at initial screening **and Screening TB Risk Assessment Questionnaire must be completed for all subjects** as defined in the Schedule of Activities (Section 1.3). Subjects with a positive or indeterminate QuantiFERON GOLD test are ineligible unless specific additional requirements are met (see Section 5.2). For subjects with a positive or indeterminate QuantiFERON GOLD test, the radiograph report should be read by a radiologist or per local requirement and the report must be reviewed by the investigator before enrollment.

On-Study

A TB Risk Assessment Questionnaire will be administered by the investigator or delegated site staff as per the Schedule of Activities (see Section 1.3) to evaluate subjects for risk and symptoms of TB. If a subject is experiencing signs or symptoms suspicious of TB or has reported changes in medical history to warrant additional on-study TB testing:

- The investigator is to follow local guidelines for the diagnosis and treatment (including prophylaxis) of active or latent TB, as applicable.
- On-study TB testing and chest X-ray may be performed and repeated at the discretion of the investigator.

- Any diagnosis of TB should be reported as a Serious Adverse Event in the Events CRF whether as active or latent TB, as applicable, based on final diagnosis.
- Subjects with confirmed active TB require permanent discontinuation of the investigational product as indicated in Section 6.2.2.1.
- It is strongly recommended to initiate treatment for latent TB. Subjects with latent TB may continue investigational product. The investigator is to contact the medical monitor to discuss the appropriateness of continuing investigational product if treatment for latent TB is not initiated.

Safety Follow--up/End of Study Visit

At the SFU/EOS visit, a QuantiFERON GOLD test will be performed in addition to the Tuberculosis Risk Assessment Questionnaire. If **at any time,** the test result is positive or indeterminate, the test may be repeated. If the repeated result is negative, the investigator may consider the subject to be negative based on the absence of symptoms and clinical judgement; if the repeat testing result is positive or indeterminate, then the subject is considered to be positive and additional assessments (eg, chest X-ray) may be performed as per local standard of care to confirm whether latent or active TB is present, and any confirmed diagnosis is to be entered as Serious Adverse Event in the Events CRF.

9. Statistical Considerations

9.1 Statistical Hypotheses

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

9.2 Sample Size Determination

A total of [redacted] subjects will be randomized in [redacted] ratio to rocatinlimab [redacted] mg (N = [redacted]) and placebo (N = [redacted]). The analyses will be descriptive in nature; therefore, the sample size is based on the expected level of precision for a range of possible positive response rates for the treatment groups. Placebo groups from previous studies in similar populations showed the positive vaccine response rates ranged from 84% to 96%. Previous studies in similar populations showed the following positive vaccine response rates:

	Vaccine Response Rates (%)			
	Active	**Placebo**	**Diff (Active – Placebo) (95% CI)**	**Half-width**
Anti-tetanus				
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
Anti-meningococcal				
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 = [redacted])	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 positive vaccine **response** rate ranges from 80% to 90%, the corresponding half-width of 95% CI **of between-group difference** will be between 12% to 9%, respectively, please see above table for reference.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Full Analysis Set	All randomized subjects. **Subjects will be analyzed according to the randomized treatment.**
Immune Response Analysis Set	All randomized subjects who have received at least 1 dose of investigational product, vaccine injection at week [redacted] and had measurement responses to vaccines at **week [redacted] and** week 24. **Subjects will be analyzed according to the actual treatment received.**
Safety Analysis Set	All subject who received at least 1 dose of investigational product. **Subjects will be analyzed according to the actual treatment received.**

9.3.1 Covariates

No covariates will be considered for the primary endpoints, and only baseline vIGA-AD stratification factor will be considered for exploratory efficacy endpoints.

9.3.2 Subgroups

No subgroup analysis is planned at this point.

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock **for the first unblinding analysis**. Below is a summary of the timing and methods for the planned statistical analyses.

9.4.1 Planned Analysis

9.4.1.1 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 complete efficacy and safety data through week 24 and additional safety data available during SFU as of the data cutoff date.

9.4.1.2 Final Analysis

The final analysis will be conducted at the end of the study when all subjects have 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.

Data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan with the expectation that all outstanding data issues are resolved ahead of the final lock.

9.4.2 Methods of Analyses

9.4.2.1 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 frequency and percentage, and corresponding 95% confidence interval (CI) where appropriate. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum.**

9.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	[redacted]

	[redacted] The vaccine responses are binary endpoints. The difference in response rates between the treatment groups (rocatinlimab/placebo) will be calculated using the Mantel-Haenszel estimate of the risk difference stratified by the randomization strata together with the 95% CI. The primary analysis of the primary endpoints will be analyzed using the respective immune response analysis set (IRS) including all randomized subjects who received at least 1 dose of investigational product, vaccine injection of the interest at week [redacted] and had measurement response to vaccine at **week** [redacted] **and** week 24.

9.4.2.3 Safety Analyses

9.4.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class, preferred term, and worst grade of severity. Tables of fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product, treatment-related adverse events, and events of interest will also be provided. Subject incidence of device-related adverse events, if applicable, may also be provided by system organ class and preferred term.

9.4.2.3.2 Laboratory Test Results

The analyses of safety laboratory results will include summary statistics over time/at selected time points by treatment group. Shifts in grades of safety laboratory values between baseline and the worst on-study value will be tabulated by treatment group, as applicable.

9.4.2.3.3 Vital Signs

The analyses of vital signs will include summary statistics of change from baseline over time by treatment group. Shifts in vital sign values between baseline and the worst on-study value will be tabulated by treatment group.

9.4.2.3.4 Electrocardiogram

The ECG measurements in this clinical study are to be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the

rigorous conditions expected to lead to meaningful evaluation of QTc data, summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials. The subject incidence of abnormal ECG diagnosis will be summarized by treatment group.

9.4.2.3.5 Antibody Formation

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

A listing of antibody results for all timepoints tested for each subject will be reported.

9.4.2.3.6 Exposure to Investigational Product

Exposure to investigational product will be summarized by treatment group. The summary of study drug exposure will include descriptive statistics for the number of study drug doses administered, and total amount of study drug exposure.

9.4.2.3.7 Exposure to Concomitant Medication

Number and proportion of subjects **receiving** will be summarized by category for each treatment group.

9.4.2.4 Other Analyses

Not applicable.

10. References

Assouline S, Buccheri V, Delmer A, et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. *Lancet Haematol*. 2016;3:e128.

Barbarot S, Auziere S, Gadkari A et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy* 2018; 73:1284-**12**93.

Blauvelt A, Simpson EL, Tyring SK, et al. Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol*. 2019;80(1):158-167.e1. doi: 10.1016/j.jaad.2018.07.048.

Bridgett C and Norén P. Stress and Atopic Dermatitis. Stress and Skin Disorders, 2019. 125**-199**.

Charman, 2004. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol*. 2004;140(12):1513-1519.

Croft M, So T, Duan W, Soroosh P. The significance of OX40 and OX40L to T-cell biology and immune disease. *Immunol Rev*. 2009;229(1):173-191.

Croft, M. Control of Immunity by the TNFR-Related Molecule OX40 (CD134). *Annu. Rev. Immunol*. 2010;28:57–78.

Davies A, Merli F, Mihaljević B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2017; 4:e272.

Eichenfield LF. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014 Feb;70 (2):338-51.

Guttman-Yassky E. Systemic immune mechanisms in atopic dermatitis and psoriasis with implications for treatment. *Exp Dermatol*. 2018 Apr;27 (4):409-417.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2019. http://www.icmje.org/

Jo CE. Facial and neck erythema associated with dupilumab treatment: A systemic review. *J Am Acad Dermatol* 2021; 84(5):1339.

Kunz B, Oranje AP, Labreze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology.* 1997;195(1):10-19.

Laughter MR, Maymone MBC, Mashayekhi S, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990-2017. *Br J Dermatol*. 2021;184:304-309.

Leo O, Cunningham A, Stern PL. Vaccine immunology. *Perspect Vaccino*. 2011;1(1):25-59. https://doi.org/10.1016/j.pervac.2011.05.002.

Lever R. The role of food in atopic eczema. *J Am Acad Dermatol*. 2001;45(1 suppl):S57-S60.

Mateos M-V, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomized, phase 3 trial. *Lancet Hametol*. 2020;7(5):e370-e380.

Merola JF, Bagel J, Almgren P, et al. 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. *J Am Acad Dermatol*. 2021;85(1):71-78.

Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab*. 2015; 66: Suppl 1: 8-16.

Rocatinlimab Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

Salek-Ardakani S, Croft M. Regulation of CD4 T-cell memory by OX40 (CD134). Vaccine. 2006 Feb 13;24 (7):872-83. doi: 10.1016/j.vaccine.2005.07.108.

Schmitt J, Langan S, Williams HW, et al. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol.* 2007;120(6):1389-1398.

Sitrin J, Suto E, Wuster A, Eastham-Anderson J, et al. The OX40/OX40 Ligand Pathway Promotes Pathogenic Th Cell Responses, Plasmablast Accumulation, and Lupus Nephritis in NZB/W F1 Mice. *J Immunol.* 2017;199 (4):1238-1249.

Simpson E, Bissonnette R, Eichenfield LF, et al. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. *J Am Acad Dermatol.* 2020;83(3):839-846.

Snast I, Reiter O, Hodak E, et al. Are Biologics Efficacious in Atopic Dermatitis? A Systematic Review and Meta-Analysis. *Am J Clin Dermatol*. 2018;19, 145–165.

Stander S. Atopic Dermatitis. *N Engl J Med*. 2021;384 (12):1136-1143.

United States Food and Drug Administration. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J EurAcad Dermatol Venereol*. 2018;32 (6):850-878.

11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
AD	atopic dermatitis
AESI	**adverse event of special interest**
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASR	annual safety report
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BIL	bilirubin
BSA	body surface area
CFR	US Code of Federal Regulations
C_{max}	maximum plasma concentration
COA	clinical outcomes assessment
COVID-19	coronavirus disease 2019
CP	CentrePoint
CRF	Case Report Form
CRO	contract research organization
CSD-AD	Consensus Sleep Diary-Atopic Dermatitis
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSUR	development safety update report
EASI	Eczema Area and Severity Index
EASI 75	achievement of ≥ 75% reduction from baseline in EASI score
ECG	electrocardiogram
[redacted]	
eCRF	electronic Case Report Form
EDC	electronic data capture
e-Diary	**electronic diary**
eGFR	estimated glomerular filtration rate
EMR	Electronic Medical Record
EOS	end of study
EOT	end of treatment

e-Tablet	**electronic tablet**
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	**Investigator's Brochure**
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IRS	immune response analysis set
IRT	interactive response technology
IV	intravenous
JAK	Janus kinase
MACE	**major adverse cardiovascular events**
MPSV4	meningococcal polysaccharide vaccine
NCT	National Clinical Trials
NRS	numeric rating scale
PCR	polymerase chain reaction
PDE4	phosphodiesterase type 4
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	**principal investigator**
POEM	Patient Oriented Eczema Measure
PRO	Patient-reported outcome
Q2W	every 2 weeks
[redacted]	[redacted]
QTc	corrected QT interval

RNA	ribonucleic acid
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	severity scoring of atopic dermatitis
SFU	safety follow-up
SOC	standard of care
SOL	sleep onset latency
TARC	thymus and activation-regulated chemokine
TB	tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
Td	tetanus and diphtheria
Tdap	tetanus, diphtheria, pertussis
Th2	T helper type 2
TIS	topical immunosuppressive
TNF	tumor necrosis factor
TST	total sleep time
ULN	upper limit of normal
US	United States
WASO	wakefulness after sleep onset

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory and/or by the local laboratory. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Central Laboratory: Chemistry	Central Laboratory: Coagulation	Central Laboratory: Urinalysis	Central Laboratory: Hematology	Other Lab Analytes
Sodium	PT/INR	Specific gravity	RBC	Central Laboratory: Drug concentration[b]
Potassium	PTT/APTT	pH	Nucleated RBC	Antidrug antibodies[b]
Chloride		Blood	Hemoglobin	Hep B surface antigen
Bicarbonate		Protein	Hematocrit	Hep C antibody
Total protein		Glucose	MCV	HIV antibody[a]
Albumin		BIL	MCH	HCV RNA
Calcium		WBC	MCHC	HBV DNA
Magnesium		RBC	RDW	QuantiFERON GOLD
Phosphorus		Epithelial cells	Reticulocytes	Serum pregnancy test
Glucose		Bacteria	Platelets	Tetanus IgG
BUN or Urea		Casts	WBC	Meningococcal IgG
Creatinine		Crystals	Differential	
Creatine Kinase			• Bands/stabs	Local Laboratory:
Uric acid			• Segmented Neutrophils	Urine Pregnancy
TBL			• Total Neutrophils	
Direct bilirubin			• Eosinophils	
ALP			• Basophils	
LDH			• Lymphocytes	
AST (SGOT)			• Monocytes	
ALT (SGPT)				
Lipids (Cholesterol, HDL, LDL, Triglycerides)				
eGFR				

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BIL = bilirubin; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TBL = total bilirubin; WBC = white blood cell count

[a] HIV assessment is recommended.

[b] Potentially unblinding laboratory analyte.

If the subject is being followed for possible drug-induced liver injury (DILI), the following analytes may be tested at the local laboratory depending on the clinical situation (see Appendix 7 [Section 11.7]).

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, RBC Count, WBC Count, WBC Differential
Coagulation	PT, INR, APTT
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis D RNA, Hepatitis E RNA, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

AB = antibody; Ag = antigen; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Data Monitoring Committee(s)

The data monitoring committee (DMC) will review all available safety data periodically and consider efficacy data in order to assess the risk/benefit profile of rocatinlimab. An Independent Biostatistics Group (IBG) will provide the analyses to the DMC. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and Data Monitoring Group will not have any direct contact with study site personnel or subjects. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master file at the conclusion of the study. Further details are provided in the DMC charter.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB)/IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all protocol amendments and changes to the informed consent document that Amgen distributes to the site. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was

obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally authorized representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

If important new information becomes available that may be relevant to the subject's consent during their participation in the study, subjects will be reconsented.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally authorized representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within [redacted] days from the previous informed consent form signature date.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research.

Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

The subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the sponsor's systems. The

sponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be prepared in accordance with Amgen's publications policy and submitted to Amgen for review. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of

data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered on the CRF.

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

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

The sponsor or designee will perform ongoing source data verification to confirm that data entered on the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently

approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case Report Forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom they have delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Response Technology (IRT) system (if used, such as subject ID and

randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the (IRB/IEC) and Amgen
- Investigational product-related correspondence including (Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable)
- [redacted], and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the trial. The EMR system should

have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of

the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Events CRF.
- The investigator must assign the following mandatory adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product
  - Action taken; and
  - Outcome of event.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization (CRO) in lieu of completion of the Events CRF.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Severity Intensity Scale for Adverse Events as shown below:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE[a]	Incapacitating with inability to work or do usual activity

[a] An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that they have reviewed the adverse event/serious adverse event and has provided an assessment of causality. For sites reporting serious adverse events via electronic data capture (EDC), the investigator or sub-investigator must confirm causality in the EDC within 72 hours of the serious adverse event being entered on the Events CRF.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. In this case, for sites reporting serious adverse events via EDC, the investigator or sub-investigator must reconfirm causality in the EDC system within 72 hours of the serious adverse event being entered on the Events CRF.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed Events CRF.
- The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool

- The primary mechanism for reporting serious adverse event will be the EDC system.
- If the EDC system is unavailable, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event Contingency Report Form) (see Figure 11-1) immediately and no later than 24 hours of the investigator's awareness of the event.
- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1).
- Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Report Form (paper-based form)

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

A **Study # 20210158** **AMG 451** **Rocatinlimab**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day_____ Month____ Year_____

Serious Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that theEvent may have been caused by IP or an Amgen device used to administer the IP? Rocatinlimab No✓ / Yes✓ <Placebo> No✓ Yes✓ <Placebo> No✓ Yes✓	**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

Serious Criteria:			
	01 Fatal	**03** Required/prolonged hospitalization	**05** Congenital anomaly / birth defect
	02 Immediately life-threatening	**04** Persistent or significant disability /incapacity	**06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	**Date Discharged** Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

		Date of Initial Dose Day Month Year	**Prior to, or at time of Event** **Date of Dose** Day Month Year	**Dose**	**Route**	**Frequency**	**Action Taken with Product** 01 Still being Administered 02 Permanently discontinued 03 Withheld	**Lot # and Serial #**
IP/Amgen Device:								
Rocatinlimab	☒ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

A **Study # 20210158** **AMG 451** **Rocatinlimab**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

<<IP/Device>> ☐ blinded ☐ open label Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

A **Study # 20210158** **AMG 451** **Rocatinlimab**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and females of childbearing potential are outlined in Section 5.2. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant during treatment and for 16 weeks after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Methods of Contraception

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks after the last dose of protocol-required therapies.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-3). The form must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks after the last dose of protocol-required therapies. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

- Any serious adverse event occurring as a result of a poststudy pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment while pregnant (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant

- **Male participants are not required to use forms of contraception during treatment with rocatinlimab. However, male participants should let their female partner know they are in this study.**
- In the event a male subject fathers a child during treatment, and for an additional 16 weeks after the last dose of protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-3) must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after the last dose of protocol-required therapies.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in the exclusion criteria (see Section 5.2).
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after the last dose of protocol-required therapies.

Figure 11-3. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20210158

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20210158

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

When permitted by local regulations, any blood, [redacted] sample collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

When permitted by local regulations and if informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the inflammatory conditions, the dose response and/or prediction of response to rocatinlimab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of [redacted] or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for subject confidentiality.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-1 antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5 x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

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

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-3) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event immediately and no later than 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Events CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 11.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 11-3 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize, or the investigational product(s) or protocol-required therapies has/have been discontinued, AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G (IgG), anti-nuclear antibody, anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents

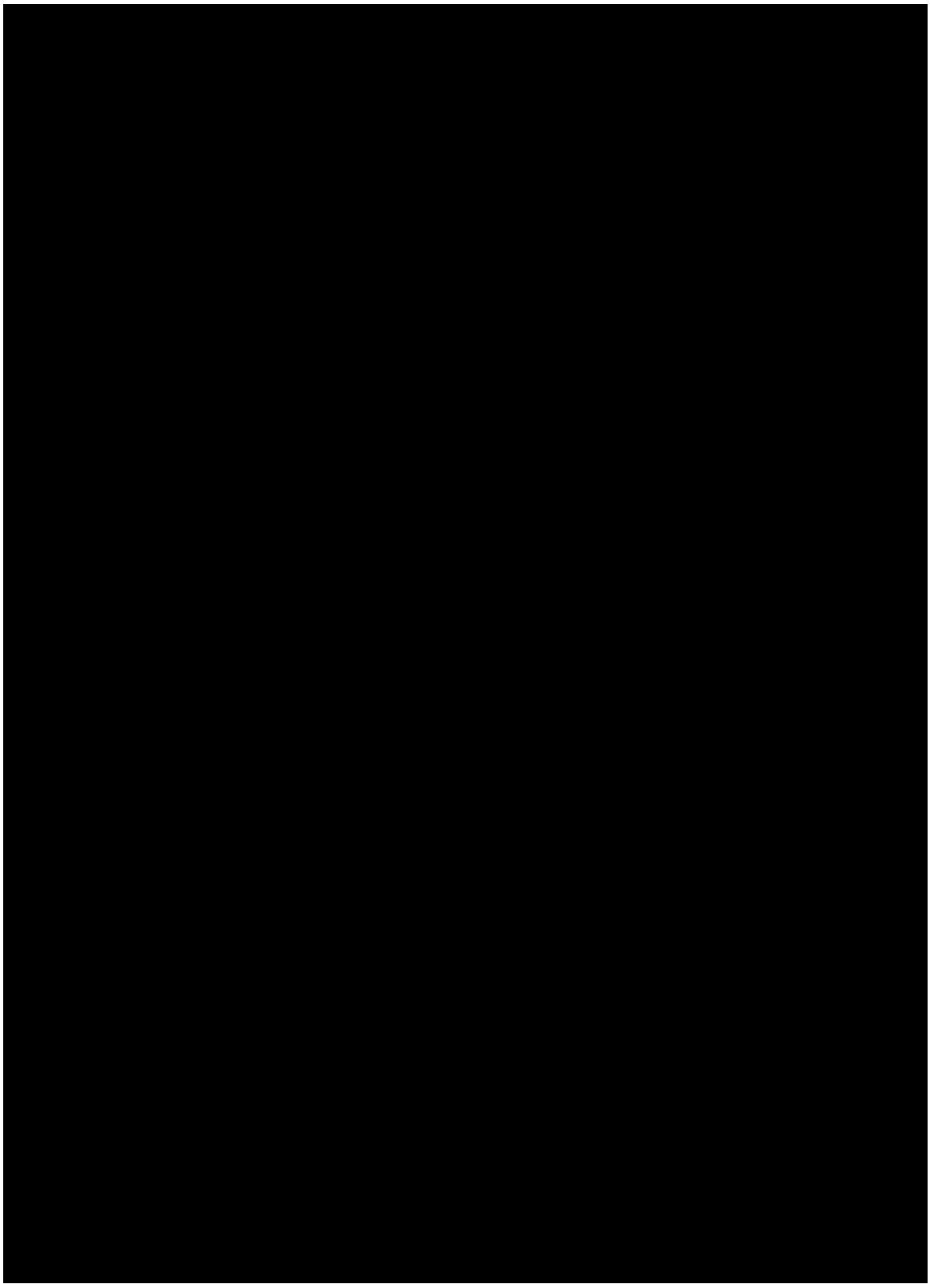
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for [redacted] if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

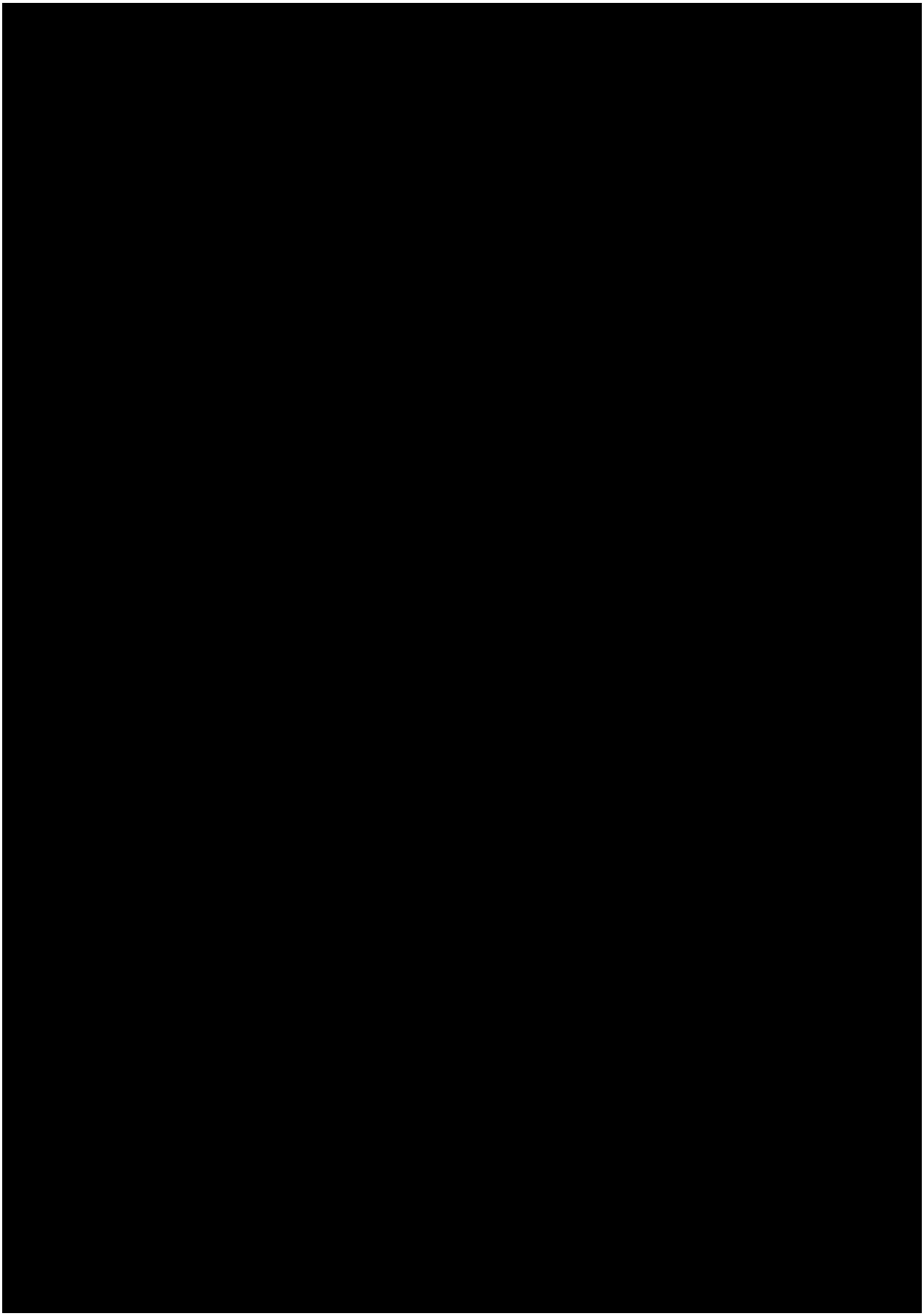
Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

11.8 Appendix 8. Topical Corticosteroids Potency Category

Table 11-4. Topical Corticosteroids Potency Category





Amendment 1

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)

Amgen Protocol Number Rocatinlimab (AMG 451) 20210158

EudraCT Number: Not available for first version

Amendment Date: 14 April 2023

Rationale:

The protocol was amended to include following updates:

- To update the screening period minimum window period of [redacted] days.
- Dosing instructions were updated to include that entire dose will be administered in a single injection.
- Provided a clarification that vaccines are not investigational products (IP) but these are studied for effect on IP.
- Corrected the language for topical and atopic rescue therapies prohibited during the first 6 weeks of treatment with IP.
- Added consensus sleep diary atopic dermatitis assessment details.
- Added activity monitor details to collect data.