

Title Page

Protocol Title:		A Phase 3, Open-label, 52-week Study to Assess the Safety, Tolerability, and Efficacy of Rocatinlimab (AMG 451) in Adolescent Subjects Aged ≥ 12 to < 18 years With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit)						
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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).

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Investigator's Agreement:

I have read the attached protocol entitled A Phase 3, Open-label, 52-week Study to Assess the Safety, Tolerability, and Efficacy of Rocatinlimab (AMG 451) in Adolescent Subjects Aged ≥ 12 to < 18 years With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit), dated **17 September 2024**, 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 Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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Signature

Name of Investigator

Date (DD Month YYYY)

Title and Role of Investigator

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 3, Open-label, 52-week Study to Assess the Safety, Tolerability, and Efficacy of Rocatinlimab (AMG 451) in Adolescent Subjects Aged ≥ 12 to < 18 years With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit)

Short Protocol Title: Phase 3 Study Assessing Rocatinlimab (AMG 451) in Adolescent Subjects With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit)

Study Phase: 3

Indication: Atopic Dermatitis

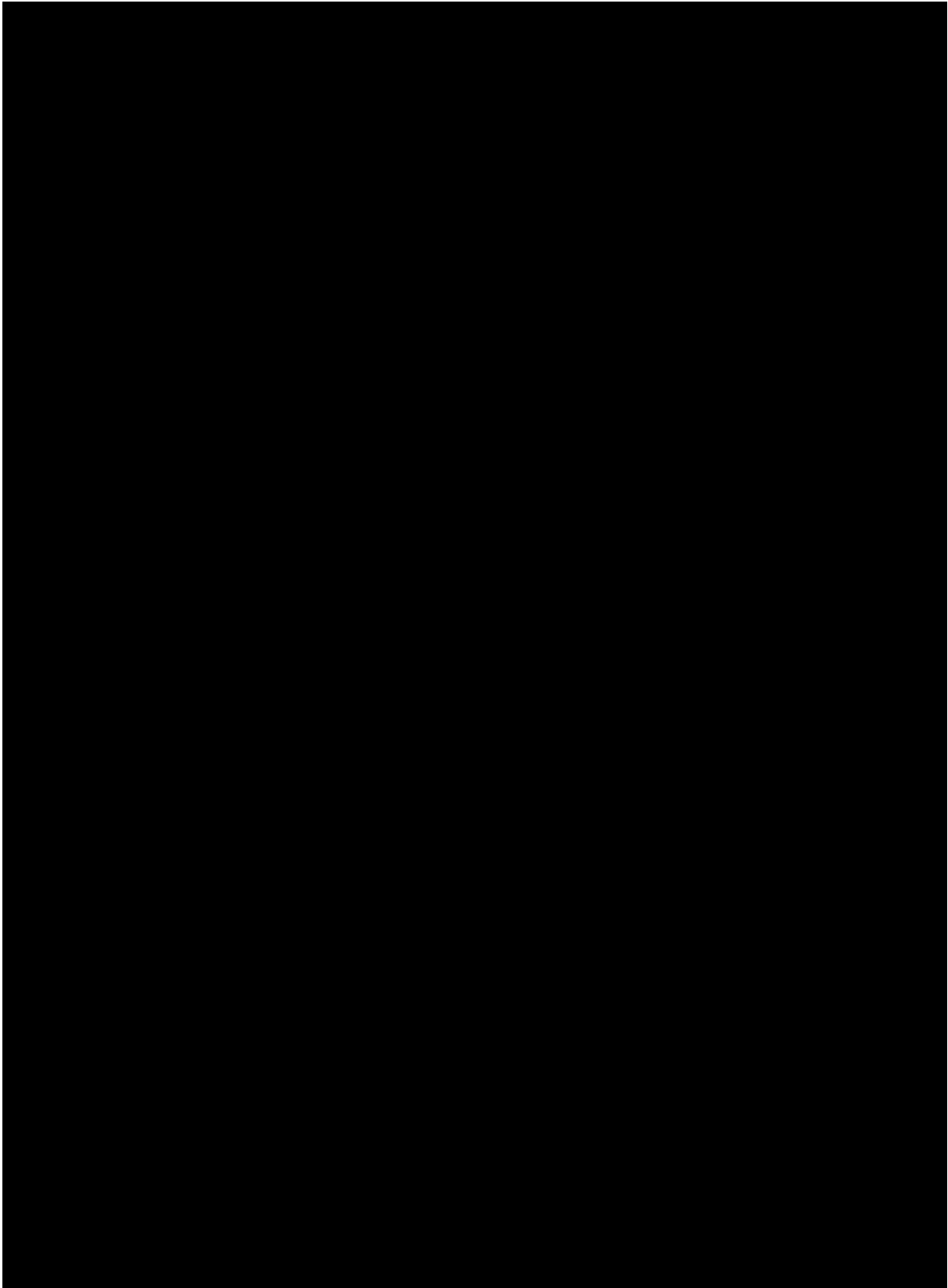
Study Rationale

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 KHK4803 and AMG 451, hereinafter referred to as rocatinlimab) is a human, non-fucosylated, 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 4803-006) evaluating the safety and tolerability of repeated doses of rocatinlimab in **participants** with moderate-to-severe AD, and conducted by Amgen partner Kyowa Kirin Co., Ltd, statistically significant improvements in percent change from baseline to week 16 in Eczema Area and Severity Index (EASI) score was observed in all rocatinlimab-treated cohorts versus placebo. In this study, all doses tested were well tolerated with an acceptable adverse event profile.

The current phase 3, open-label study will be conducted in combination with topical therapy in adolescent **participants** presenting with moderate-to-severe AD with inadequate response to topical medications. The study is designed to evaluate and

provide supportive evidence of the safety, tolerability, and efficacy of rocatinlimab in the adolescent population.

Benefit/Risk Assessment



[REDACTED]

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

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

Primary Estimand

Not applicable for primary safety endpoint.

Overall Design

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

subcutaneously at [REDACTED] mg for 52 weeks with one additional dose at week 2. Prior advanced therapy, including biologic or targeted-small molecules (eg, Janus kinase [JAK] inhibitors), is allowed with an adequate washout period.

Participants will undergo an initial screening visit to confirm eligibility requirements.

Participants who do not meet all the eligibility requirements at initial screening and day 1 pre-enrollment will be considered screen failures. **Participants** may be allowed to re-screen once.

A protocol defined [REDACTED] will apply to **participants** who do not demonstrate an adequate benefit after [REDACTED] of treatment with the investigational product.

Participants may continue investigational product treatment if any of the following criteria are met:

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

Participants who do not meet any of these criteria after 36 weeks of investigational product treatment will discontinue investigational product at that visit (ie, end of treatment [EOT] visit) and complete the safety follow-up visit [REDACTED] weeks after the last dose of investigational product.

Rescue Therapies for AD

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.

Use of TCS of high or super-high potency, topical phosphodiesterase type 4 (PDE4) inhibitors, topical JAK inhibitors, phototherapy, or systemic therapies for AD during the 52-week study will be considered use of rescue therapy in the analysis ([Table 6-3](#)). A list of TCS and their assigned potencies can be found in [Table 11-4](#). Allowed rescue therapies are those approved for treatment of AD as well as local standard of care.

Participants may continue investigational product if there is concurrent use of topical rescue therapies (excluding topical JAK inhibitors) or phototherapy. **Participants** must permanently discontinue investigational product if there is use of prohibited therapies, systemic corticosteroids, conventional nonbiologic, 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 Participant Discontinuation

Participants who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 52 for the evaluation of endpoints (see [Section 1.3](#)).

Participants who permanently discontinue investigational product and do not complete the remaining study visits through week 52 should complete an EOT visit following the last dose of the investigational product (see W52/EOT in [Section 1.3](#)).

Safety Follow-up

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

The maximum study duration for a single **participant** will be approximately 68 weeks, including a screening period of up to 30 days, a 52-week treatment period, and a SFU visit [REDACTED] weeks after the last possible dose of investigational product at week 48.

The overall study design is described by a study schema in [Section 1.2](#). A full list of endpoints are defined in [Section 3](#).

Number of Participants

Approximately 170 adolescent **participants** will be enrolled in the study.

Summary of Participant Eligibility Criteria

- Males or females aged ≥ 12 to < 18 years at day 1 with a diagnosis of AD (according to American Academy of Dermatology Consensus Criteria; Eichenfield et al, 2014), that has been present for at least 12 months before signing informed consent. Prior to informed consent, history of inadequate response to TCS of medium to higher potency (refer to [Table 11-4](#)) (with or without TCI as appropriate).
- Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to Validated Investigator Global Assessment for Atopic Dermatitis [IGA] score of 0 = clear to 2 = mild) despite treatment with a daily regimen of TCS of medium to higher potency ($\pm$ TCI as appropriate), applied for at least 28 days or the maximum duration recommended by the product prescribing information (eg, 14 days for super-high potent TCS), whichever is shorter.
- Presence of moderate-to-severe AD at both initial screening and day 1 pre-enrollment, defined as EASI score ≥ 12 , vIGA-AD™ score ≥ 3 (on the 0 to 4

vIGA-AD scale, in which 3 is moderate and 4 is severe) and $\geq 10\%$ body surface area (BSA) of AD involvement.

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

Treatments

Rocatinlimab will be administered subcutaneously at [REDACTED] mg every 4 weeks (Q4W) for 52 weeks with one additional dose at week 2.

Statistical Considerations

Approximately 170 adolescent **participants** will be enrolled in the study. Assuming the dropout rate during the first 24 weeks being 10% and the subsequent 28 weeks being 20% of the remaining **participants** at week 24, it is expected that approximately 122 adolescent **participants** will be exposed to 52 weeks of rocatinlimab [REDACTED] mg.

All analyses will be descriptive. For categorical endpoints, the descriptive statistics will contain frequency, percentage, and corresponding 95% 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.

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

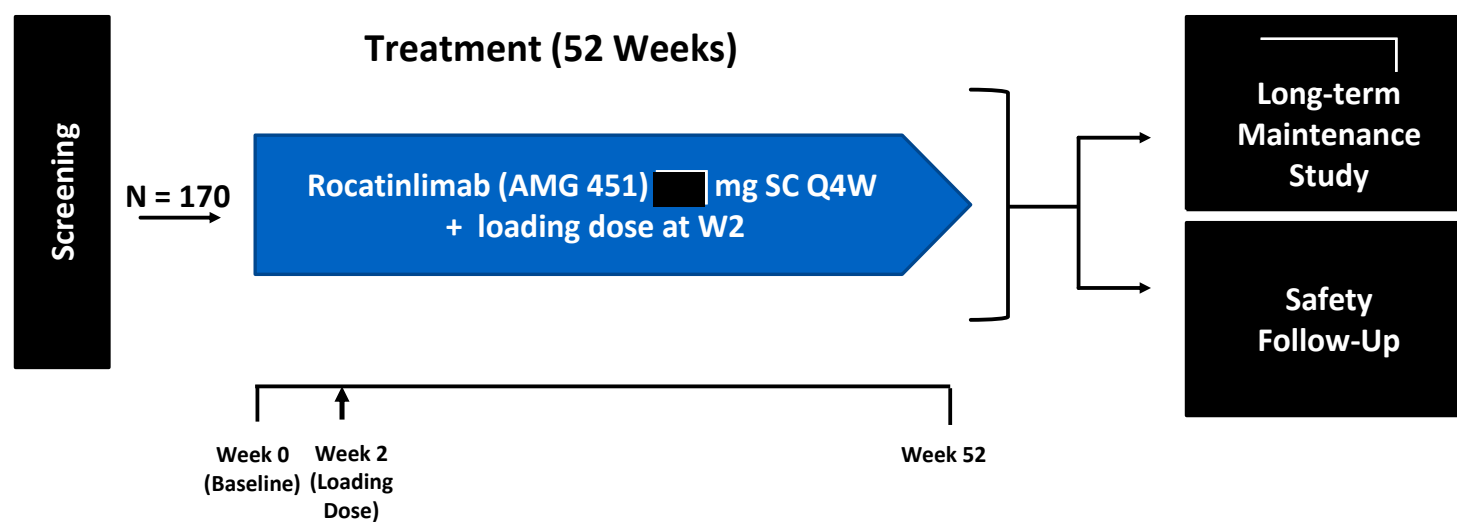
Statistical Hypotheses

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

Sponsor Name: Amgen

1.2 Study Schema

Figure 1-1. Study Schema



Q4W = every 4 weeks; SC = subcutaneous; W = week(s)

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities

Procedure	Screening Period		Treatment Period ^a																	EOS/SFU ^{a,b} (+ 3d)	Unsched Visit ^d
	Screening (Up to 30 Days Before Day 1)	Day 1 Pre- Enrollment	Day 1 ^b Post- Enrollment																		
GENERAL AND SAFETY ASSESSMENTS																					
Informed consent	X																				
Inclusion and exclusion criteria	X	X ^c																			
Demographics	X																				
Physical examination ^p	X							X			X			X			X	X	X		
Vital signs ^e	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X	X						X			X			X				X	X		
Body weight	X	X						X			X			X				X	X		
Medical history	X																				
Dermatologic medical history	X																				
Immunologic medical history	X																				
Cardiovascular medical history	X																				
Medication history	X																				
Prior treatment for AD ^f	X	X																			
Substance use history ^g	X																				

Table 1-1. Schedule of Activities

Procedure	Screening Period		Treatment Period ^a																	EOS/SFU ^{a,b} (+ 3d)	Unscheduled Visit ^d
	Screening (Up to 30 Days Before Day 1)	Day 1 Pre- Enrollment	Day 1 ^b Post- Enrollment																		
ECG	X								X			X							X		X
Evaluation of childbearing potential (menarche) ^j	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiovascular risk factors			X																		
Adverse events			X	X	x	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events ^j	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X
Screening TB risk assessment questionnaire		X																			
On-study TB risk assessment questionnaire									X			X			X					X	
Pubertal maturation self-assessment (Tanner Staging) ^k			X									X							X		
LABORATORY ASSESSMENTS^l																					
Coagulation	X																				X
HIV, Hepatitis B and C screening ^m	X																				X
Hepatitis B DNA (reactivation monitoring only) ⁿ												X							X		X
Serum pregnancy test (participants of childbearing potential only) ^o	X																				X
Urine pregnancy test (participants of childbearing potential only) ^o		X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X				X	X		X		X			X		X		X	X	X
Chemistry	X						X	X	X			X			X				X	X	X

Table 1-1. Schedule of Activities

Procedure	Screening Period			Treatment Period ^a																	EOS/SFU ^{1a,b} (+ 3d)	Unshed Vist ^{1d}
	Screening (Up to 30 Days Before Day 1)	Day 1 Pre- Enrollment	Day 1 ^b Post- Enrollment																			
LABORATORY ASSESSMENTS ¹																						
Urinalysis ^a	X																					X
QuantiFERON GOLD ^r	X																		X			X
EFFICACY/CLINICAL OUTCOME ASSESSMENTS -ASSESSED BY INVESTIGATOR																						
vIGA-AD	X	X				X	X	X	X	X	X	X	X	X	X ^y	X	X	X	X			X
EASI	X	X				X	X	X	X	X	X	X	X	X	X ^y	X	X	X	X			X
EFFICACY/CLINICAL OUTCOME ASSESSMENTS -ASSESSED BY PARTICIPANT ¹																						
HADS	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ACT test only for participants with a history of asthma			X				X	X	X	X	X	X	X	X	X	X	X	X	X			X
STUDY TREATMENT																						
Mental health recommendation review ^z		X				X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Ab = antibody; [REDACTED]; AD = atopic dermatitis; BSA = body surface area; D = day; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; [REDACTED] EOS = end of study; EOT = end of treatment; HADS = Hospital Anxiety and Depression Scale; HBsAg = hepatitis B Surface Antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; JAK = Janus kinase; PK = pharmacokinetic; SFU = safety follow-up; TB = tuberculosis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; unsched = unscheduled; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis; W = week

^a **Participants** who permanently discontinue investigational product for any reason are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 52 for evaluation of endpoints. **Participants** who permanently discontinue investigational product and do not complete the remaining study visits through week 52 should complete an EOT visit following the last dose of investigational product (see W52/EOT in [Table 1-1](#)). A safety follow-up visit is required [REDACTED] weeks after the last dose of investigational product for all **participants** who do not continue into the long-term maintenance study (Study [REDACTED]).

^b [REDACTED]

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

^d Unscheduled visits may occur at any time point during the treatment period, and only those assessments deemed necessary should be performed at the discretion of the investigator.

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

^f Prior TCS/TCIs that were being taken for AD from 12 months prior to initial screening through enrollment, and prior systemic therapies (including topical JAK inhibitors) that were being taken for AD from 10 years prior to initial screening through enrollment should be collected.

^g Alcohol, recreational drugs, and tobacco use.

^h [REDACTED]

ⁱ If the **participant** is confirmed as being of childbearing potential at screening or at any time on-study, no additional childbearing potential assessments are needed and they should switch to urine pregnancy tests.

^j 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. Please refer to Section [8.4.5](#) for additional details.

^k All **participants** (or their caregivers, if developmentally appropriate) will perform a Pubertal Maturation Self-assessment (Tanner Staging; Appendix 9 Section [11.9](#)) on site at day 1. Only **participants** who have not reached Tanner Stage 5 in both categories at day 1 need to be further assessed according to the Schedule of Activities until reaching Tanner Stage 5 in both categories.

^l To be collected predose.

^m Hepatitis B DNA testing will be performed for **participants** with positive HBsAg and/or HBV core Ab.

ⁿ For **participants** with positive HBsAg and/or HBV core Ab at initial screening. Any additional testing may be performed per investigator's discretion.

^o Additional on-study pregnancy testing may be performed at the investigator's discretion if there is suspicion that a **participant** is pregnant or per local laws and regulations.

^p 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.

^q Additional urinalysis can be performed on-study at the investigator's discretion per standard of care.

^r Refer to Section [8.9.1](#) for additional information on tuberculosis assessments.

^s [REDACTED]

^t Clinical Outcome Assessments should be assessed prior to any other assessments at each visit.

^u Only for **participants** who achieve vIGA-AD score of 1.

^v [REDACTED]

w

l

y) [REDACTED], participants whose EASI score has not had at least 25% improvement in EASI score from baseline or at least 1 point improvement in vIGA-AD from baseline will discontinue investigational product at that visit (ie, EOT visit) and complete the safety follow-up visit [REDACTED] weeks after the last dose of investigational product. Refer to Section [6.2.2.1](#) for additional information.

^z Investigator must review latest central mental health professional 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 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 KHK4803 and AMG 451, hereinafter referred to as rocatinlimab) is a human, non-fucosylated, 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 4803-006) evaluating the safety and tolerability of repeated doses of rocatinlimab in **participants** with moderate-to-severe AD, and conducted by Amgen partner Kyowa Kirin Co., Ltd, statistically significant improvements in percent change from baseline to week 16 in Eczema Area and Severity Index (EASI) score was observed in all rocatinlimab-treated cohorts versus placebo. In this study, all doses tested were well tolerated with an acceptable adverse event profile.

The current phase 3, open-label study will be conducted in combination with topical therapy in adolescent **participants** presenting with moderate-to-severe AD with inadequate response to topical medications. The study is designed to evaluate and provide supportive evidence of the safety, tolerability, and efficacy of rocatinlimab in the adolescent population.

2.2 Background

2.2.1 Disease

Atopic dermatitis 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, TCIs, 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 (IL)-4R α subunit shared by the IL-4 and 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 (**EU**) 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 ■ mg every 1 or 2 weeks fail to reach achievement of $\geq 75\%$ reduction from baseline in EASI score (EASI 75) at week 16 (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, 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.

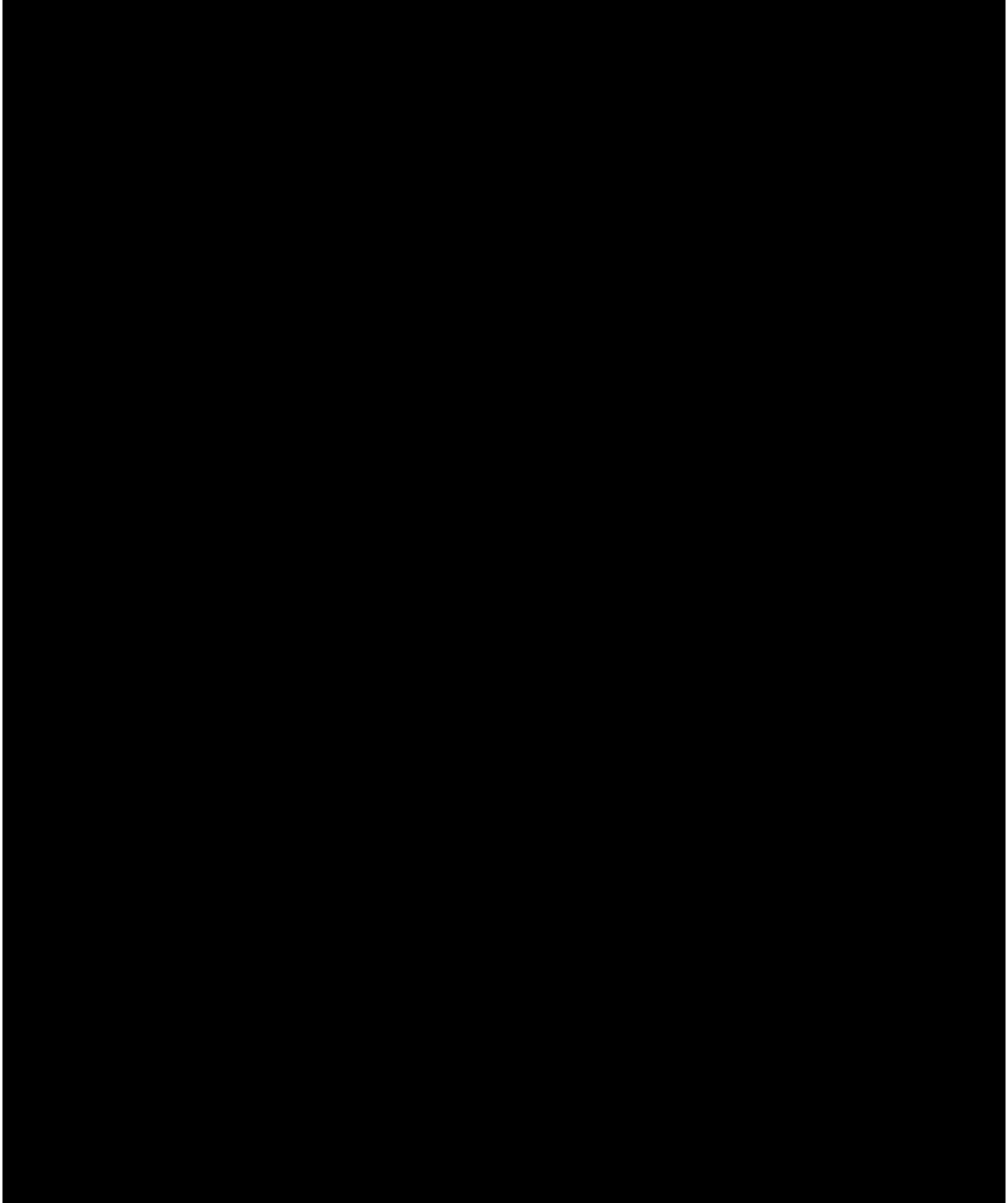
2.2.2 Amgen Investigational Product Background: Rocatinlimab

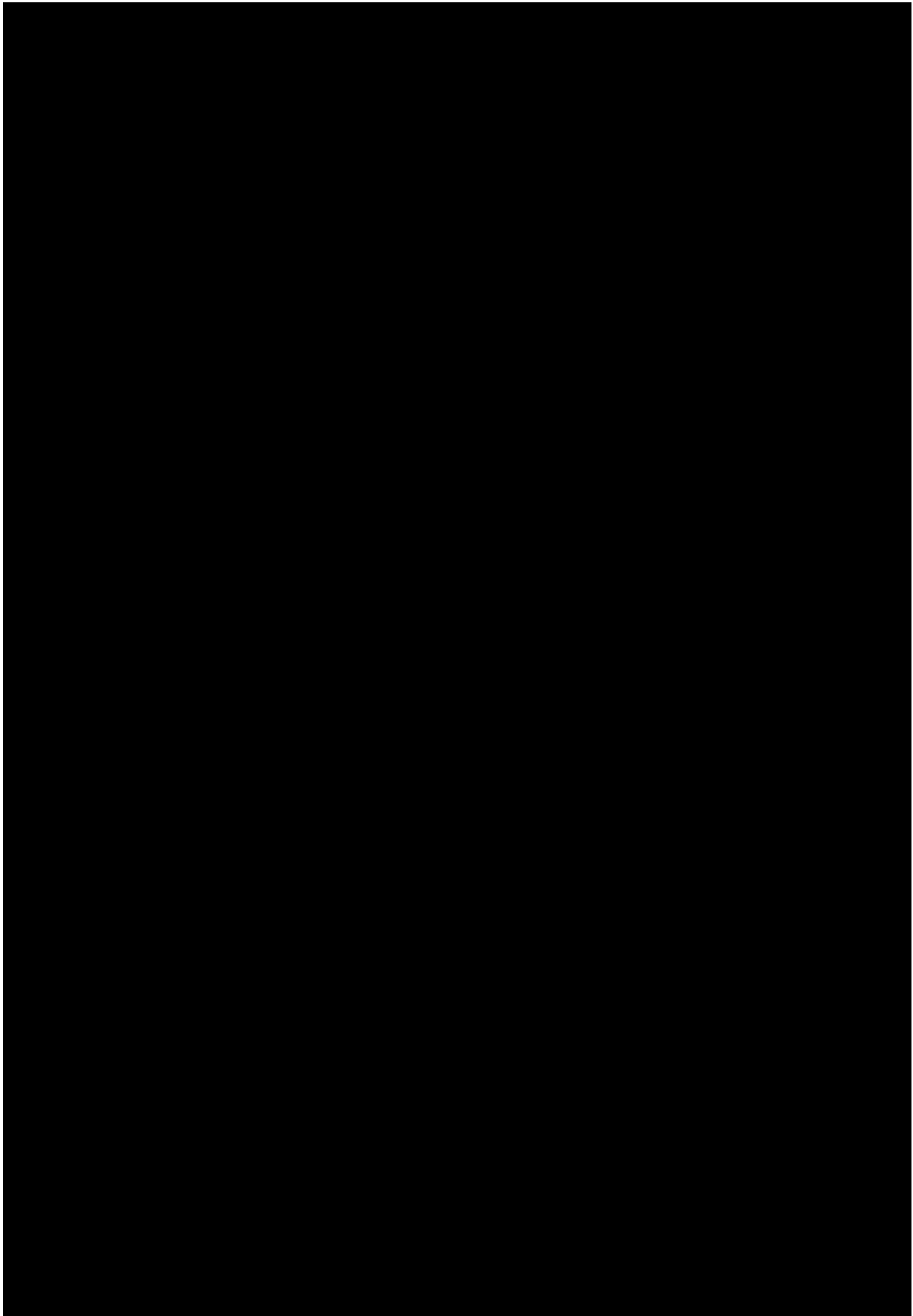
Rocatinlimab is an investigational human, non-fucosylated IgG1 mAb specific for inhibiting OX40/OX40L interaction to treat the chronic inflammation in AD and other

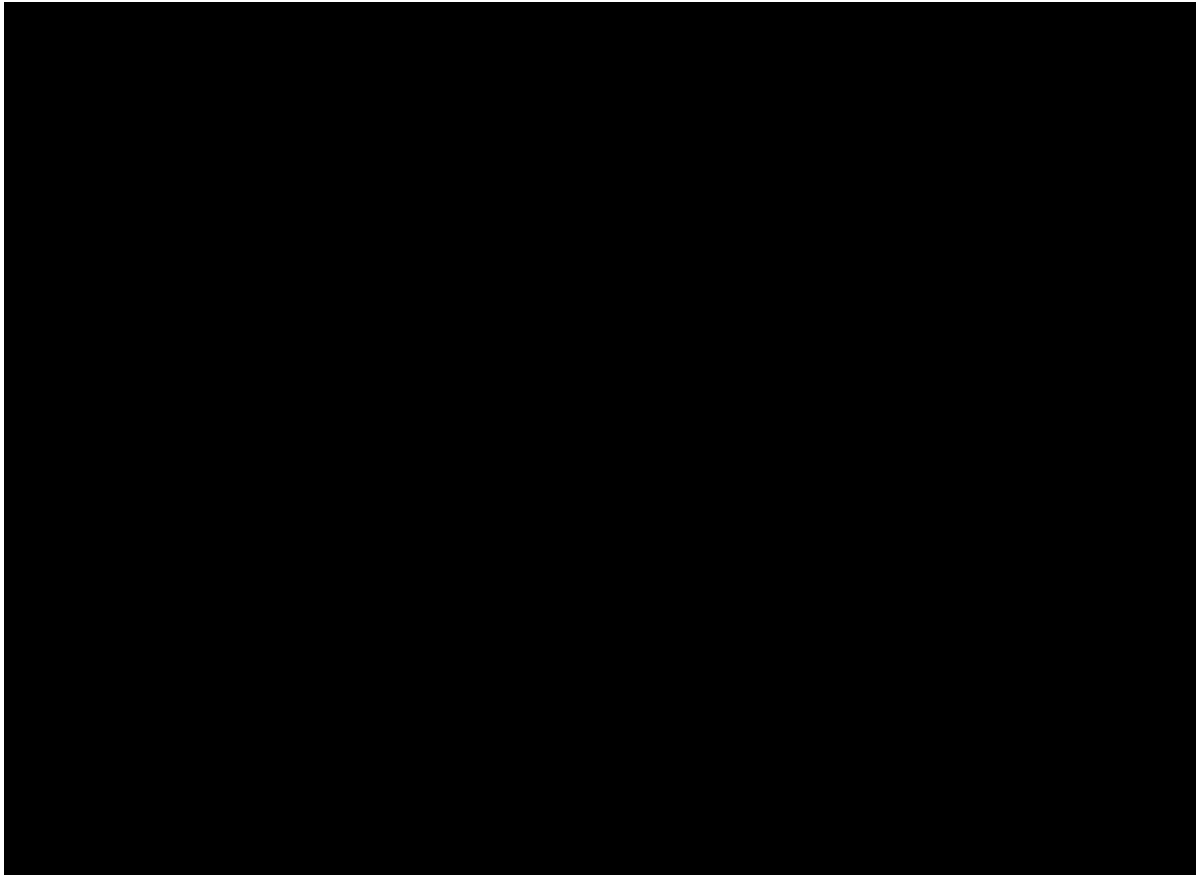
autoimmune diseases. To date, the efficacy and safety of intravenous (IV) and subcutaneous (SC) rocatinlimab has been evaluated in 5 early phase clinical studies.

A detailed description of the chemistry, pharmacology, efficacy, and safety of rocatinlimab is provided in the investigator's brochure (IB).

2.3 Benefit/Risk Assessment







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.

Participants 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.

Participants enrolled in this study are permitted to receive vaccinations for COVID-19 as described in Section [6.7.2](#).

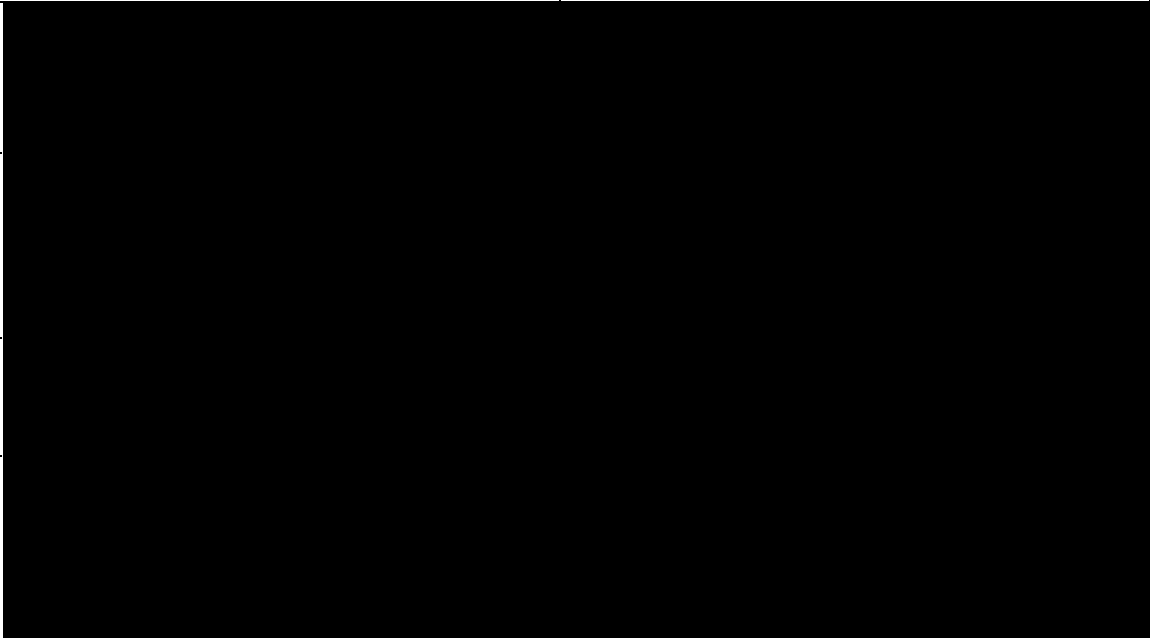
3. Objective(s) and Endpoint(s)/Estimand(s)

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

Primary Estimand

Not applicable for primary safety endpoint.

Exploratory	
To describe the clinical response of rocatinlimab [REDACTED] mg treatment regimen using validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™)	- Achieving a vIGA-AD score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline at assessment time points - Achieving a vIGA-AD score of 0 (clear) with ≥ 2-point reduction from baseline (vIGA-AD 0) response at assessment time points
To describe the clinical response of rocatinlimab [REDACTED] mg treatment regimen at assessment time points, using vIGA-AD with an additional assessment of morphology	Achieving vIGA-AD 1 response with presence of only barely perceptible erythema or vIGA-AD 0 response (revised Investigator's Global Assessment [rIGA™] 0/1) at assessment time points
To describe the clinical response of rocatinlimab [REDACTED] mg treatment regimen using Eczema Area and Severity Index (EASI)	- Achieving $\geq 50\%$ reduction from baseline in EASI score (EASI 50) at assessment time points - Achieving $\geq 75\%$ reduction from baseline in EASI score (EASI 75) at assessment time points - Achieving $\geq 90\%$ reduction from baseline in EASI score (EASI 90) at assessment time points

	• Achieving 100% reduction from baseline in EASI score (EASI 100) at assessment time points • Percent change from baseline in EASI score at assessment time points
	

4. Study Design

4.1 Overall Design

This is a phase 3, open-label, 52-week study to evaluate and provide supportive evidence of the safety, tolerability, and efficacy of rocatinlimab in adolescent **participants** with moderate-to-severe AD with inadequate response to topical medications in combination with topical therapy. Rocatinlimab will be administered subcutaneously at  mg Q4W for 52 weeks with one additional dose at week 2. Prior advanced therapy including biologic or targeted-small molecules (eg, Janus kinase [JAK] inhibitors) is allowed with an adequate washout period.

Participants will undergo an initial screening visit to confirm eligibility requirements.

Participants who do not meet all the eligibility requirements at initial screening and day 1 pre-enrollment will be considered screen failures. **Participants** may be allowed to rescreen once.

Participants may be eligible to enroll in a long-term maintenance study (Study ).

A protocol defined [REDACTED] will apply to **participants** who do not demonstrate an adequate benefit after 36 weeks of treatment with the investigational product.

Participants may continue investigational product treatment if any of the following criteria are met:

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

Participants who do not meet any of these criteria after 36 weeks of investigational product treatment will discontinue investigational product at that visit (ie, end of treatment [EOT] visit) and complete the safety follow-up visit [REDACTED] weeks after the last dose of investigational product.

Rescue Therapies for AD

Topical corticosteroids (TCS) of low-to-medium potency with or without 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.

Use of TCS of at least high potency, topical PDE4 inhibitors, topical JAK inhibitors, phototherapy, or systemic therapies for AD during the 52-week study will be considered use of rescue therapy in the analysis (Table 6-3). A list of TCS and their assigned potencies can be found in Table 11-4. Allowed rescue therapies are those approved for treatment of AD as well as local standard of care.

Participants may continue investigational product if there is concurrent use of topical rescue therapies (excluding topical JAK inhibitors) or phototherapy. **Participants** must be permanently discontinued if there is use of prohibited therapies, systemic corticosteroids, conventional nonbiologic, non-targeted immunosuppressive systemic therapies, biologics, or 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 Participant Discontinuation

Participants who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 52 for the evaluation of endpoints (see Section 1.3).

Participants who permanently discontinue investigational product and do not complete the remaining study visits through week 52 should complete an end of treatment (EOT) visit following the last dose of the investigational product (see W52/EOT in Section 1.3).

Safety Follow-up

A safety follow-up (SFU) visit is required [REDACTED] weeks after the last dose of investigational product for all **participants** who do not continue into the long-term maintenance study (Study [REDACTED]).

The maximum study duration for a single **participant** will be up to approximately

[REDACTED]
[REDACTED]
[REDACTED]

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

Approximately 170 adolescent **participants** will be enrolled in the study.

Individuals participating in this clinical investigation shall be referred to as “participants” (certain defined variable names may use the term “subjects”, ie “subject identification number”). For the sample size justification, see Section 9.2.

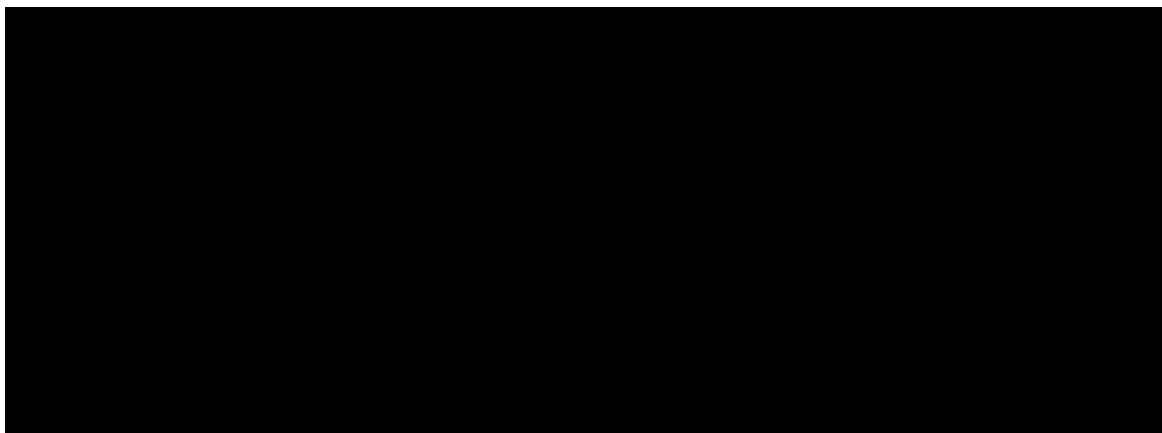
4.2 Patient Input into the Study Design

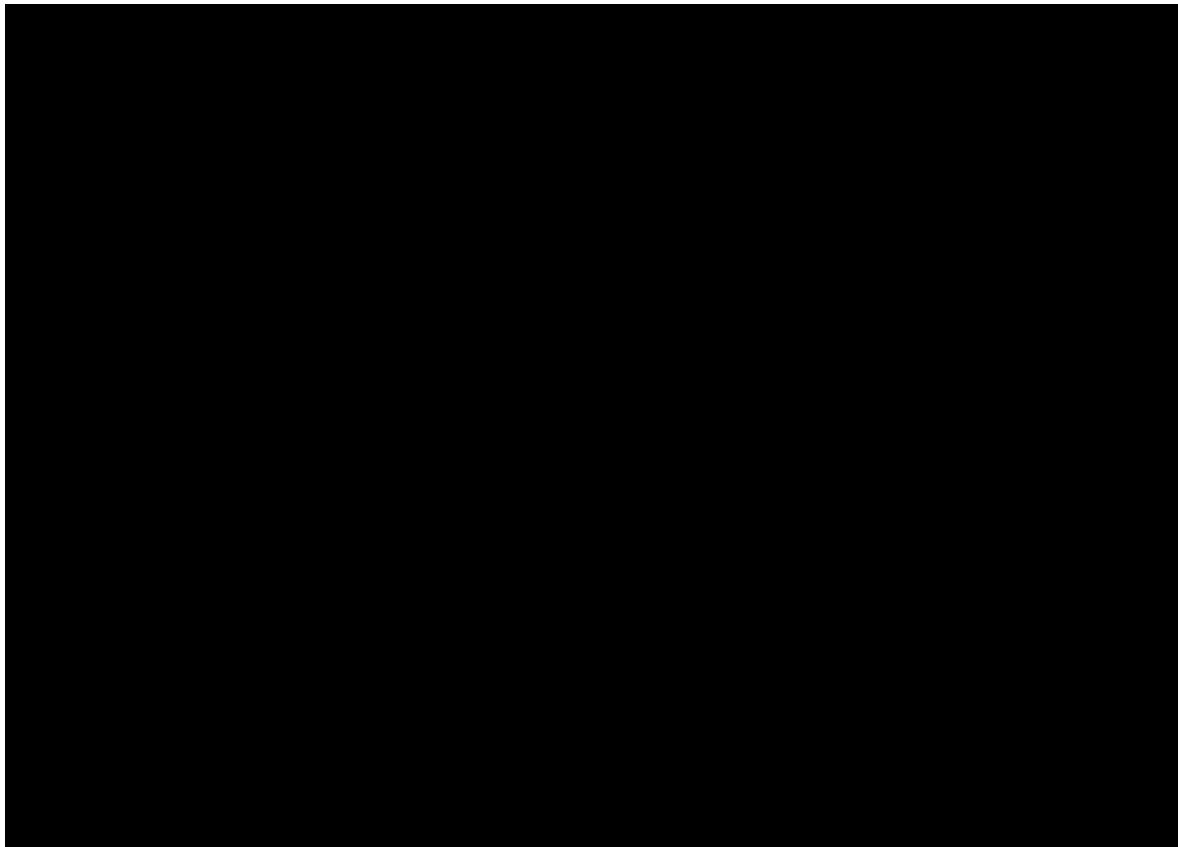
Patient input was not obtained for this study.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

This study will be used to investigate rocatinlimab [REDACTED] mg Q4W with an additional dose of [REDACTED] mg on week 2 for a total treatment duration of 52 weeks and obtain safety data for 170 adolescent **participants**.





4.4 End of Study

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

An individual **participant** 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 maximum total study duration for an individual **participant** is approximately 68 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 the screening period through the day 1 pre-enrollment 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.

The sponsor will monitor the study population baseline characteristics during enrollment. If necessary, the sponsor may restrict enrollment of certain populations in order to ensure the appropriate distributions of **participant** characteristics.

5.1 Inclusion Criteria

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

- 101 **Participant's** legally authorized representative (if allowed, depending on the country concerned) has provided informed consent when the **participant** is legally too young to provide informed consent and the **participant** has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.
- 102 Age ≥ 12 to < 18 years at day 1.
- 114 **Participant** has a diagnosis of AD (according to American Academy of Dermatology Consensus Criteria [Eichenfield et al, 2014]) that has been present for at least 12 months before signing of informed consent.
- 104 Body weight ≥ 40 kg at screening.
- 105 Body weight ≥ 40 kg at day 1 pre-enrollment.
- 115 Prior to informed consent, history of inadequate response to TCS of medium to higher 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).
 - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA score of 0 = clear to 2 = mild) despite treatment with a daily regimen of TCS of medium to higher potency ($\pm$ TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever is shorter.
 - **Participants** with previous systemic treatment for AD are also considered as inadequate responders to topical treatments and are potentially eligible to be included in the study after appropriate washout.
- 116 EASI score ≥ 12 at initial screening.
- 117 EASI score ≥ 12 at day 1 pre-enrollment.
- 109 vIGA-AD score ≥ 3 (on the 0 to 4 vIGA-AD scale, in which 3 is moderate and 4 is severe) at initial screening.
- 110 vIGA-AD score ≥ 3 (on the 0 to 4 vIGA-AD scale, in which 3 is moderate and 4 is severe) at day 1 pre-enrollment.
- 111 $\geq 10\%$ BSA of AD involvement at initial screening.
- 112 $\geq 10\%$ BSA of AD involvement at day 1 pre-enrollment.

5.2 Exclusion Criteria

Participants 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.
- 202 History of major immunologic reaction (eg, serum sickness, anaphylaxis, or anaphylactic reaction) to any other biologic product or any excipient of rocatinlimab.
- 203 Known sensitivity to any of the products or components to be administered during dosing.
- 204 Diagnosis of a helminth parasitic infection within 6 months prior to day 1 pre-enrollment that had not been treated with or had failed to respond to standard of care therapy.
- 205 Evidence of human immunodeficiency virus (HIV) infection or positive for HIV antibodies at initial screening or current acquired, common variable or inherited, primary or secondary immunodeficiency.
- 206 Positive for hepatitis C virus (HCV) antibody at initial screening with confirmed positive HCV RNA.
- 207 Active and non-virally suppressed hepatitis B infection at initial screening, defined as detectable hepatitis B DNA polymerase chain reaction (PCR) test in a **participant** with detectable hepatitis B Surface Antigen (HBsAg) and/or antibodies to hepatitis B core (anti-HBc). **Participants** with detectable HBsAg are required to be virally suppressed with an approved hepatitis B antiviral therapy during the study.
- 231 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 pre-enrollment per Screening TB risk assessment questionnaire provided by Amgen:
- No symptoms of TB
 - 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 pre-enrollment
- 209 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.
- 232 Active chronic or acute infection requiring treatment with systemic antibiotics, antiviral, antiparasitic, antiprotozoal, or antifungals which has not completely resolved, or for which therapy has not been completed, within 4 weeks before day 1 pre-enrollment.

- 211 Superficial skin infections within 2 weeks before day 1 pre-enrollment.
- 212 Severe depression, poorly controlled schizophrenia, or **participants** who have had an inpatient psychiatric admission within the last year. **Participants** who are receiving a psychiatric treatment regimen must have been on a stable treatment for at least 8 weeks prior to study day 1 pre-enrollment.

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- 215 Any of the following laboratory abnormalities at initial screening:

- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2.5 times the upper limit of normal (ULN)
- Neutrophil count < 1.5 x 10³/μL

- 233 History of New York Heart Association class III/IV heart failure; uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg) at initial screening; or inadequately treated cardiovascular conditions at initial screening including: cardiomyopathy, major congenital heart disease, or second- or third-degree atrioventricular block.

- 234 Recent cardiovascular events including: cerebrovascular accident, myocardial infarction, coronary stenting, or unstable angina within 6 months of day 1 pre-enrollment.

Prior/Concomitant Therapy

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

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

- 235 Treatment with any of the following medications or therapies within 4 weeks or 5 half-lives, whichever is longer, prior to day 1 pre-enrollment.

- 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 nonbiologic, non-targeted systemic immunosuppressants
- Phototherapy
- Oral or topical JAK inhibitors

- 230 Treatment with any of the following agents within 1 week before day 1 pre-enrollment:
- Topical phosphodiesterase type 4 (PDE4) inhibitors
 - Other topical immunosuppressive agents (not including TCS/TCI)
 - Combination topical agents containing a high- or super-high potency corticosteroid or any of the above components
- 220 Treatment with live virus including live attenuated vaccination 12 weeks prior to day 1 pre-enrollment. Inactive vaccination (eg, non-live or nonreplicating agent), including COVID-19 vaccination, is allowed.

Prior/Concurrent Clinical Study Experience

- 221 Previous participation in a study including rocatinlimab (formerly KHK4083 or AMG 451) or any therapy selectively targeting OX40/OX40L and receipt of active investigational product.
- 236 Currently receiving treatment in another investigational device or drug study, or less than 30 days (■ weeks for Japan) or 5 half-lives, whichever is longer, since ending treatment on another investigational device or drug study(ies) prior to day 1 pre-enrollment. Other investigational procedures while participating in this study are excluded.

Other Exclusions

- 223 **Participants** of childbearing potential unwilling to use protocol specified method of contraception see Appendix 5 (Section 11.5) during treatment and for an additional ■ weeks after the last dose of investigational product.
- 224 **Participants** who are breastfeeding or who plan to breastfeed while on study through ■ weeks after the last dose of investigational product.
- 225 **Participants** planning to become pregnant while on study through ■ weeks after the last dose of investigational product.
- 226 **Participants** of childbearing potential with a positive pregnancy test assessed at initial screening and day 1 pre-enrollment by a highly sensitive serum or urine pregnancy test, respectively.
- 228 **Participant** 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) to the best of the **participant** and investigator's knowledge.
- 229 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 **participant** 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 **participants** 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 (Bridgett 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 **participants** should be encouraged to adhere to usual activity and avoid any activities known to affect their AD.

5.4 Participant Enrollment

Before **participants** 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 **participant** information and/or recruitment material, if applicable (see Section 11.3).

The **participant** or the **participant's** legally authorized representative (if allowed, depending on the country concerned) must personally sign and date the IRB/IEC and Amgen-approved informed consent before commencement of study-specific procedures. Additionally, where required, an age-appropriate informed assent form must be signed by the **participant**.

Each **participant** who enters into the screening period for the study (defined as when they [or their legally acceptable representative, if allowed, depending on the country concerned] 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 **participant** throughout the clinical study and must be used on all study documentation related to that **participant**.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a **participant** is rescreened.

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

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

5.5 Screen Failures

Screen failures are defined as **participants** (or their legally acceptable representative [if allowed, depending on the country concerned]) 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], [REDACTED], placebo, combination product(s), or medical device(s) intended to be administered to a study **participant** 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]
[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

Table 6-1. Investigational Products

Study Treatment Name	Amgen Investigational Product: ^a Rocatinlimab
Dosage Formulation	■ mg/mL Supplied as a single-use, preservative free solution for injection
Unit Dose Strength(s)	■ mg per vial
Dosage Level(s)	Rocatinlimab ■ mg Q4W with an additional dose given at week 2
Route of Administration	SC Injection
Accountability	The quantity of investigational product administered per vial, start date/time, and lot number of investigational product are to be recorded on each participant's CRF(s).
Dosage Preparation	Information regarding dose preparation/administration will be provided to the site.

CRF = case report form; Q4W = every 4 weeks; SC = subcutaneous

^a Rocatinlimab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.



6.1.3 Medical Devices

Medical devices will not be used in this study.

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

Non-Amgen noninvestigational 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.

6.1.4 Other Intervention Procedures

There are no other interventional procedures in this study.

6.1.5 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 product provisioned and/or repackaged/modified by Amgen.

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

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

6.1.6.1 Atopic Dermatitis Rescue therapy

Topical and systemic rescue therapies for AD are discouraged during the study period with the investigational product (see Section 6.7.3).

6.1.6.2 Other Excluded/Discouraged Therapies for Atopic Dermatitis or Related Conditions

The use of the following therapies is discouraged at any time during the study.

However, **participants** 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 $\geq 20\%$, ammonium lactate $\geq 12\%$, or salicylic acid $\geq 3\%$.
- Antihistamines for treatment of pruritus.

6.1.6.3 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. Therapeutics for Non-AD Related Conditions

Therapies if given for non-AD-related conditions	Restrictions	Requires Temporary Interruption or Permanent Discontinuation of Investigational Product
• Live vaccines • Any investigational product in another device or drug study	Always prohibited	Permanent Discontinuation
• Systemic corticosteroids (eg, oral, IV, 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 temporary interruption to avoid concurrent administration • No temporary interruption required if systemic corticosteroid treatment and adequate washout period (5 half-lives) have completed by next investigational product dose If treatment duration > 2 consecutive weeks • Permanent discontinuation

Therapies if given for non-AD-related conditions	Restrictions	Requires Temporary Interruption or Permanent Discontinuation of Investigational Product
Conventional immunosuppressive or immunomodulatory agents (nonbiologic, nontargeted), 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
• Immunosuppressive or immunomodulatory biologics for the treatment of non-AD autoimmune, inflammatory, or allergic diseases (eg, dupilumab, interleukin inhibitors, anti-IgE, 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

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

6.2 Dose Modification

6.2.1 Dose-group/cohort Study Escalation/De-escalation and [REDACTED]

Not applicable.

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

6.2.2.1 Amgen Investigational Product: Rocatinlimab

A protocol defined [REDACTED] will apply to **participants** who do not demonstrate an adequate benefit after [REDACTED] weeks of treatment with the investigational product.

Participants may continue investigational product treatment if any of the following criteria are met:

- At least 25% improvement in EASI from baseline
- At least 1 point improvement in vIGA-AD from baseline

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

In addition, 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.

- Severe depression as assessed by the investigator. The investigator should immediately refer the **participant** 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 $\leq 0.5 \times 10^9/L$ 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 investigation 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 **participant**. 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. **Participants** 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 **participants** with the Site to Patient process. Site to Patient specific training will be provided and support materials for the sites and **participants** 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 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Participants who meet eligibility criteria and enroll in the study will be assigned to treatment with rocatinlimab.

6.4.2 Blinding

This is an open-label study; procedures to blind treatment assignment are not applicable.

6.5 Treatment Compliance

When **participants** are dosed at the site, they will receive rocatinlimab 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 in the CRF.

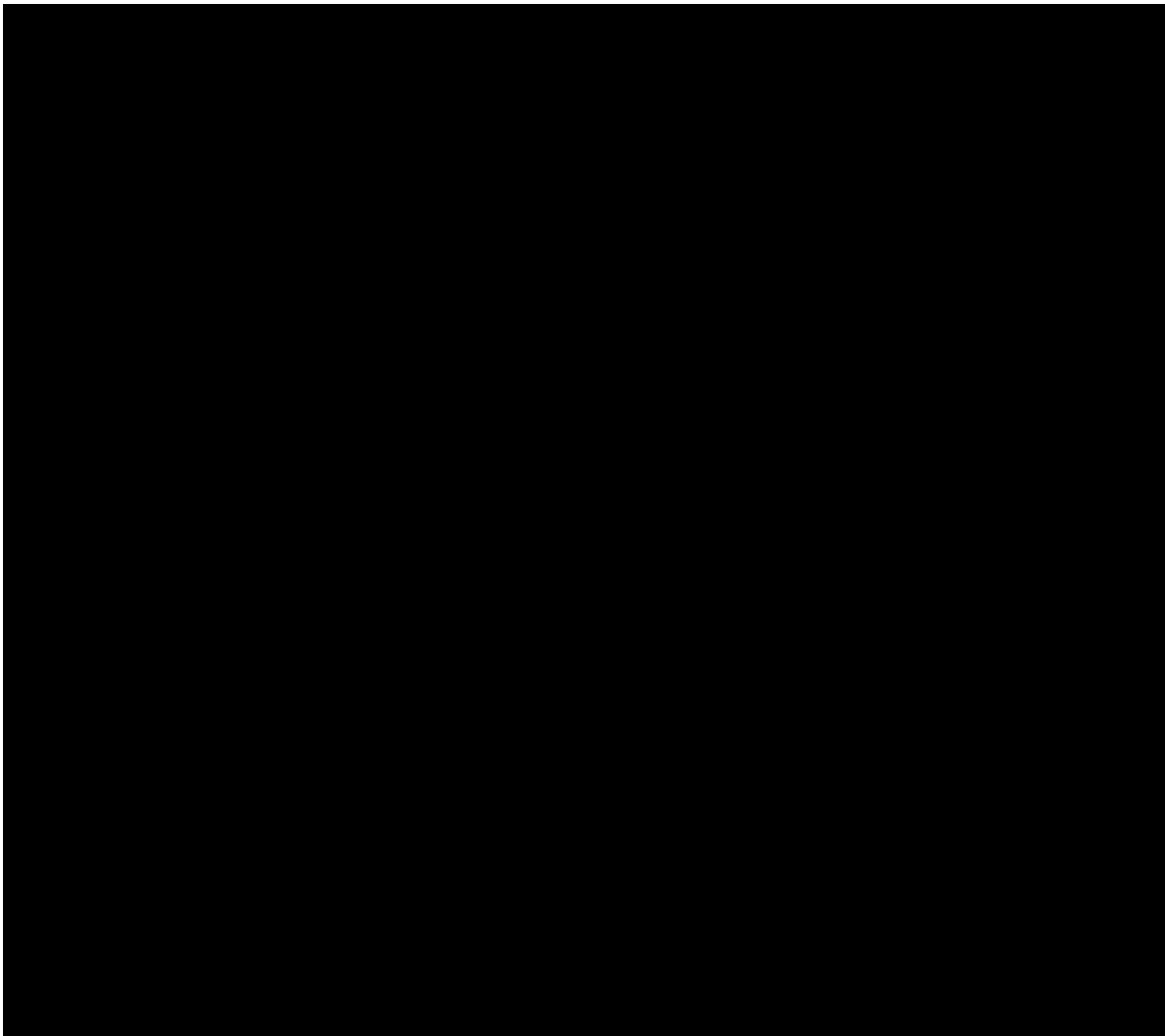
6.6 Treatment of Overdose

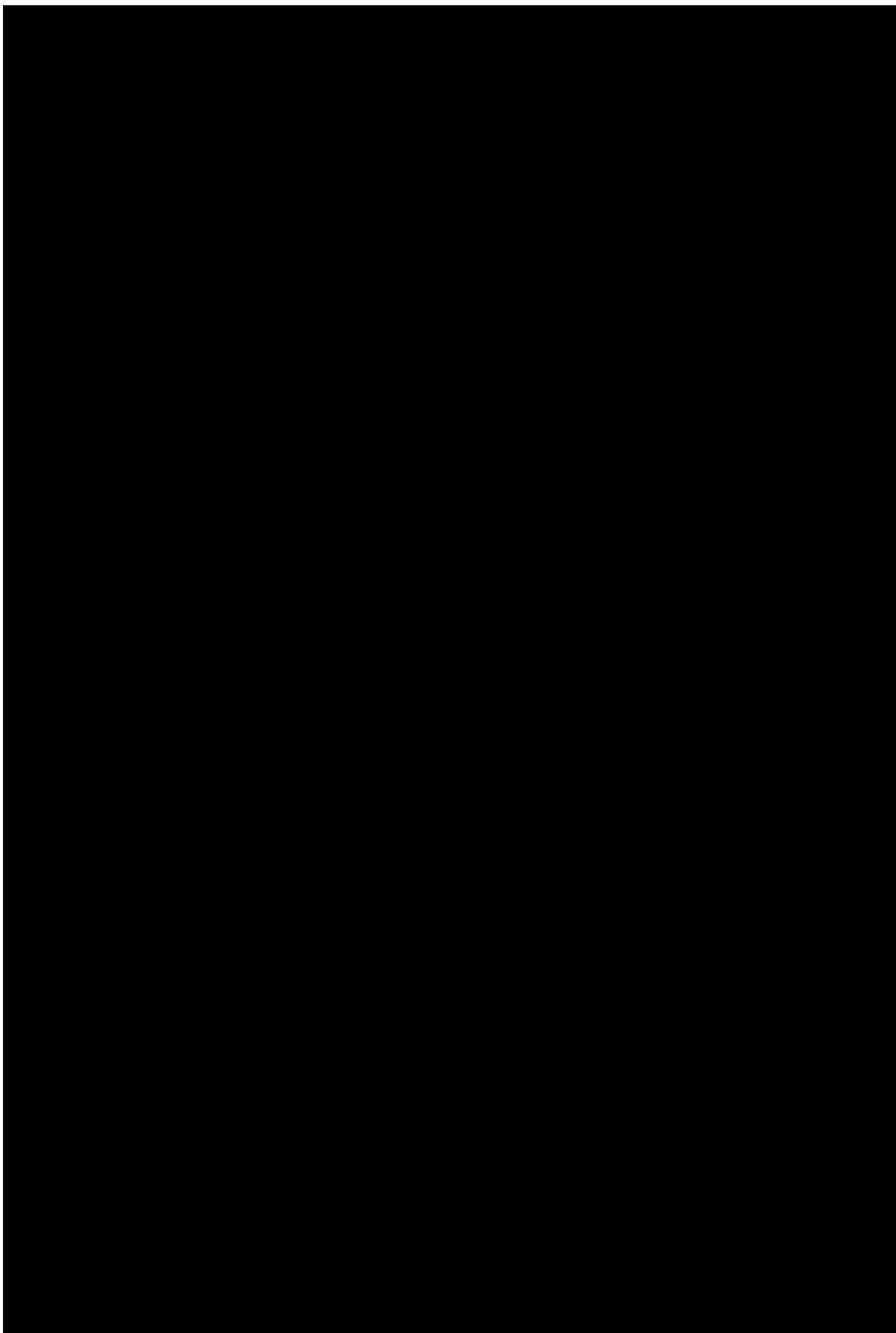
Overdose, defined for the purpose of this study as any dose above the highest dose specified in this protocol (see Section 6.1), is anticipated to be low. Rocatinlimab will be administered under medical supervision by qualified personnel and the maximum possible dose to be administered in case of dosing preparation error is [REDACTED] mg.

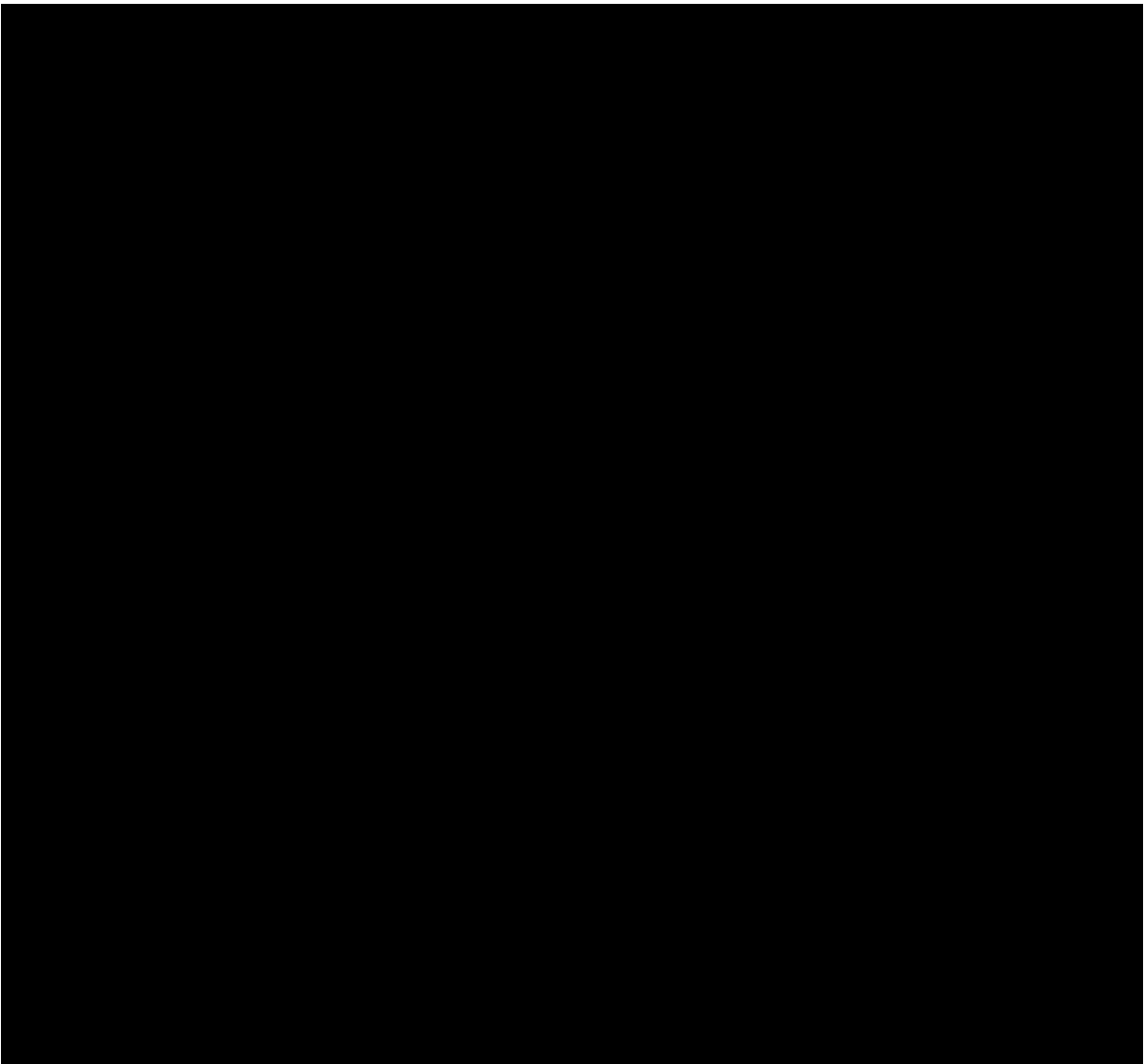
Treatment of overdose of rocatinlimab consists of general supportive measures directed to the observed clinical effects. There is no known specific antidote for overdose of rocatinlimab. In case of suspected overdose, the investigator should:

- 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.

6.7 Prior and Concomitant Treatment







6.7.3 Rescue Therapies for Atopic Dermatitis or Related Conditions

In the event of worsening and/or unacceptable symptoms of AD, rescue with standard of care therapies may be given if deemed necessary by the investigator. Rescue therapies are defined as therapies concordant with AD treatment and are listed in [Table 6-3](#).

Allowed rescue therapies are those approved for treatment of AD as well as local standard of care. It is recommended to use topical rescue therapies before considering using systemic rescue.

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

Table 6-3. Rescue Therapy for AD

Rescue Therapy for AD	If deemed necessary, when permitted for use	Requires Temporary Interruption or Permanent Discontinuation of Investigational Product
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) • Combination agents including TCS of high- or super high potency, PDE4 inhibitors, or other topical immunosuppressive agents • Phototherapy	Use is discouraged during study, however permitted if deemed necessary.	No
• Systemic corticosteroids (eg, oral, IV or intramuscular)	Use is discouraged during study, however permitted if deemed necessary. NOTE: Recommend consideration of topical rescue therapies first	Permanent discontinuation

Rescue Therapy for AD	If deemed necessary, when permitted for use	Requires Temporary Interruption or Permanent Discontinuation of Investigational Product
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) • Oral JAK inhibitors (eg, upadacitinib, baricitinib, abrocitinib) • Topical JAK inhibitors (eg, ruxolitinib cream)	At least 16 weeks after discontinuation of the investigational product NOTE: Recommend use of topical rescue therapies before escalating to systemic rescue therapy	Permanent Discontinuation

AD = atopic dermatitis; IV = intravenous; JAK = Janus kinase; PDE4 = phosphodiesterase type 4;
 TCS = topical corticosteroids

^a A full list of topical corticosteroids and potency category is provided in Section 11.8.

7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

Participants (or a legally authorized representative) have the right to withdraw from investigational product, [REDACTED] and/or 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 **participant(s)** from investigational product, [REDACTED] device, and/or 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

Participants (or a legally authorized representative [if allowed, depending on the country concerned]) can decline to continue receiving investigational product and/or [REDACTED] 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 **participant** the appropriate processes for discontinuation from investigational product and/or [REDACTED] and must discuss with the **participant** 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 **participant's** medical records. **Participants** are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 52 after permanent discontinuation of investigational product for evaluation of endpoints (see Section 1.3). **Participants** who have discontinued investigational product and/or [REDACTED] and/or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that **participants** remain on-study to ensure safety surveillance and/or collection of outcome data.

Reasons for early removal from investigational product 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](#))
- protocol-specified criteria (see Section [6.2.2.1](#) related to [REDACTED])
- pregnancy

7.2 Participant Discontinuation/Withdrawal From the Study

Withdrawal of consent for a study means that the **participant** does not wish to, or is unable to continue further study participation. **Participant** 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 **participant** appropriate procedures for withdrawal from the study and must document the **participant's** decision to withdraw in the **participant's** medical records. **Participants** who are withdrawn or removed from treatment or the study will not be replaced.

If a **participant** 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 **participant** from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

7.3 Lost to Follow-up

A **participant** will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and the **participant's** legally acceptable representative (if allowed, depending on the country concerned) is unable to be contacted by the study site.

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

- The site must attempt to contact the **participant's** legally acceptable representative (if allowed, depending on the country concerned) and reschedule the missed visit as soon as possible and counsel the **participant's** legally acceptable representative (if allowed, depending on the country concerned) on the importance of maintaining the assigned visit schedule and ascertain whether or not the **participant** and/or the **participant's** legally acceptable representative (if allowed, depending on the country concerned) wishes to and/or is able to continue in the study.
- In cases in which the **participant** is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the **participant's** legally acceptable representative (if allowed, depending on the country concerned) (where possible, 3 telephone calls and, if necessary, a certified letter to the **participant's/participant's** legally acceptable representative's (if allowed, depending on the country concerned) last known mailing address or local equivalent methods). These contact attempts are to be documented in the **participant's** medical record.
- If the **participant's** legally acceptable representative (if allowed, depending on the country concerned) continues to be unreachable, the **participant** will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For **participants** 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 **participant** 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 **participant** is to continue or discontinue study treatment.

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

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Informed consent/assent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the **participant's** legally acceptable representative (if allowed, depending on the country concerned) has signed the informed consent form and the **participant** has provided assent (where required), the site will register the **participant** in the IRT and screen the **participant** in order to assess eligibility for participation. The screening window is up to 30 days.

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

If a **participant** has not met all eligibility criteria at both initial screening and day 1 pre-enrollment visits, the **participant** will be registered as a screen fail. Screen fail **participants** may be eligible for rescreening 1 time.

Rescreen **participants** must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the **participant** is registered as rescreened, a new screening window will begin. **Participants** will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 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 investigational product is to be administered last during each visit that it is required.

Participants may be eligible to enroll in a long-term maintenance study (Study [REDACTED]).

8.1.3 End of Treatment

Participants who permanently discontinue investigational product for any reason are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 52 for evaluation of endpoints (see Section 1.3). **Participants** who permanently discontinue investigational product and do not complete the remaining study visits through week 52 should complete an EOT visit following the last dose of investigational product (see W52/EOT in Section 1.3).

8.1.4 Safety Follow-up

A SFU visit is required [REDACTED] weeks after the last dose of investigational product for all **participants** who do not continue into the long-term maintenance study (Study [REDACTED]). An additional SFU visit will not be required for **participants** who discontinue investigational product but who complete the remaining study visits for at least [REDACTED] weeks after the last dose of investigational product before or at week 52.

8.1.5 End of Study

Refer to Section 4.4 for the end of study definition.

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

8.2 General Assessments

8.2.1 Informed Consent

All **participants** or their legally authorized representative (if allowed, depending on the country concerned) must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

If approved by the IRB/EC, **participants'** legally acceptable representative (if allowed, depending on the country concerned) may be consented and **participant** may be assented remotely. In the case of remote consent/assent, the following procedures should be followed:

- The **participant's** legally acceptable representative (if allowed, depending on the country concerned) should be sent a blank informed consent form/informed consent addendum via mail or email.
- A member of the study site team (investigator or designee) will call the **participant's** legally acceptable representative (if allowed, depending on the country concerned) to walk through the document via phone and answer questions. The time and date of the phone conversation should be recorded in the **participant's** medical record.

- The **participant's** legally acceptable representative (if allowed, depending on the country concerned) should sign the informed consent form/informed consent addendum and **participant** sign the assent after all questions are answered and return the original or scanned copy via mail or email, respectively. The date and time of the **participant's** legally acceptable representative (if allowed, depending on the country concerned) consent should be recorded in the medical record. The **participant's** legally acceptable representative (if allowed, depending on the country concerned) should take a photograph of the signature pages and send them to the person conducting the informed consent/assent discussion.
- The person who conducted the informed consent/assent discussion should then sign and date the informed consent/assent form/informed consent addendum, when received.
- A fully signed version of the informed consent/assent form/informed consent addendum should be provided to the **participant's** legally acceptable representative (if allowed, depending on the country concerned).

8.2.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with **participant** safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on [REDACTED] of the investigational product.

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 **participant'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

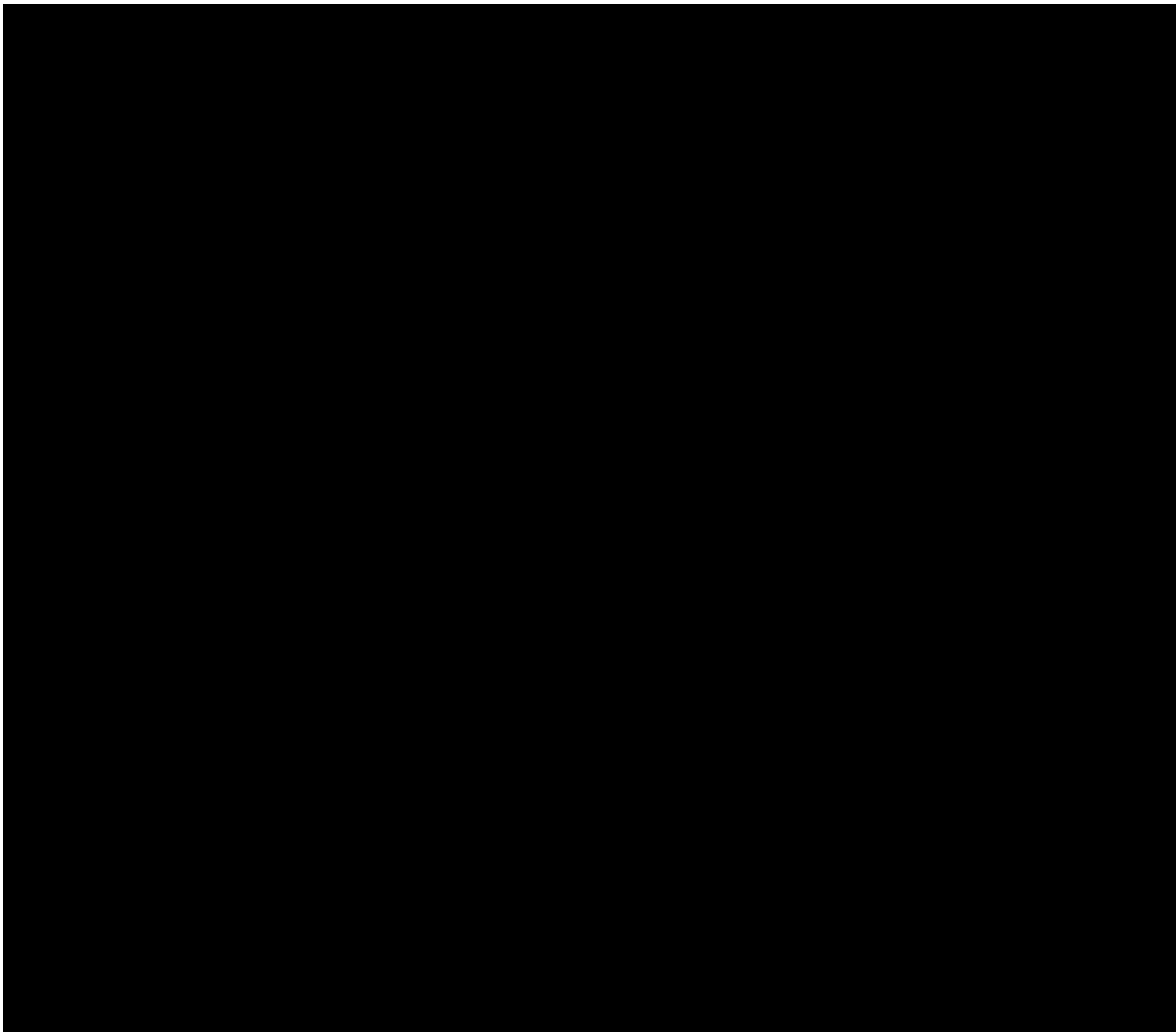
A complete physical examination will be conducted at screening and cover general appearance, dermatological, head, ear, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. At subsequent study visits, a symptom-directed physical examination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

8.2.5 Physical Measurements

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

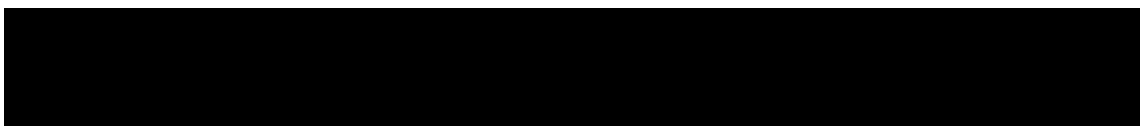
8.2.6 Substance Abuse History

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



8.2.8 Mental Health Assessment

As AD is associated with higher 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.



Screening

Investigators must review relevant **participant** data at screening, including, but not limited to, medical history, prior and current medications, substance use, Hospital Anxiety and Depression Scale (HADS) responses, and [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] The investigator should immediately refer the **participant** for local mental health assessment and treatment as per local standard of care. **Participants** ineligible due to depression and/or [REDACTED] or behavior may be rescreened once after one year or 6 months respectively.

On-study

[REDACTED]

Participants with severe depression as assessed by the investigator, are to discontinue investigational product (Section [6.2.2.1](#)) and should immediately be referred to mental health assessment and treatment, as per local standard of care.

[REDACTED]

Any psychiatric adverse event is to be followed and reported in the Events CRF as provided in Section 8.4.5. Referral to mental health services must be entered by the investigator in the Other Action Taken field of the corresponding adverse event.

8.2.10 Pubertal Maturation Self-assessment (Tanner Staging)

All **participants** (or their caregivers, if developmentally appropriate) will perform a Pubertal Maturation Self-assessment (Tanner Staging; Appendix 9 Section 11.9) on site at day 1. Only **participants** who have not reached Tanner Stage 5 in both categories at day 1 need to be further assessed according to the Schedule of Activities (Section 1.3) until reaching Tanner Stage 5 in both categories. The self-assessment form contains illustrations of the 5 different stages of pubertal maturation based on breast development and pubic hair (for females) and genitals and pubic hair (for males). No physical exam by a health care provider will be performed to assess puberty maturation except where required by local regulation.

8.3 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 **participant** 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 time point according to the Schedule of Activities (see Section 1.3), clinical outcome reports (COAs) are to be assessed prior to any other assessment.

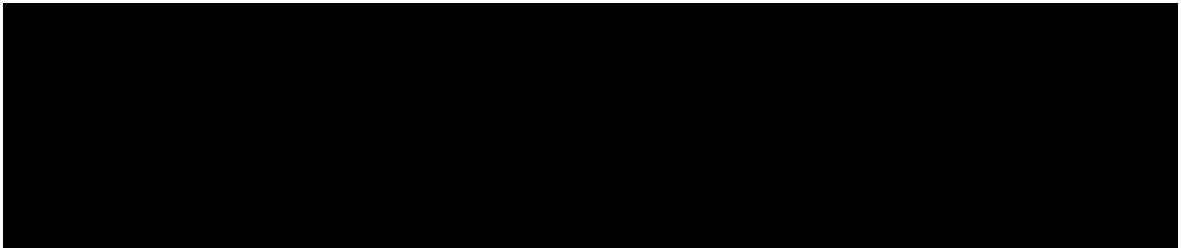
8.3.1 Assessments Completed by Investigator

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

8.3.1.1 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 ©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.

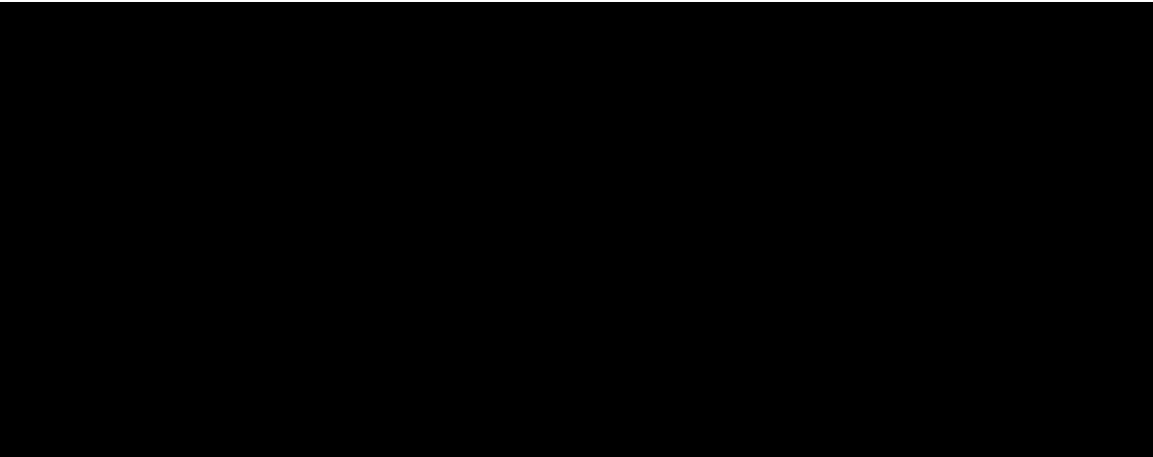
The vIGA-AD will be assessed at the time points shown in the Schedule of Activities (see Section 1.3). Whenever possible, the vIGA-AD should be assessed by the same investigator at each visit to reduce the inter-rater variability.



8.3.1.3 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-rate variability.



8.3.2 Assessments Completed by Participant

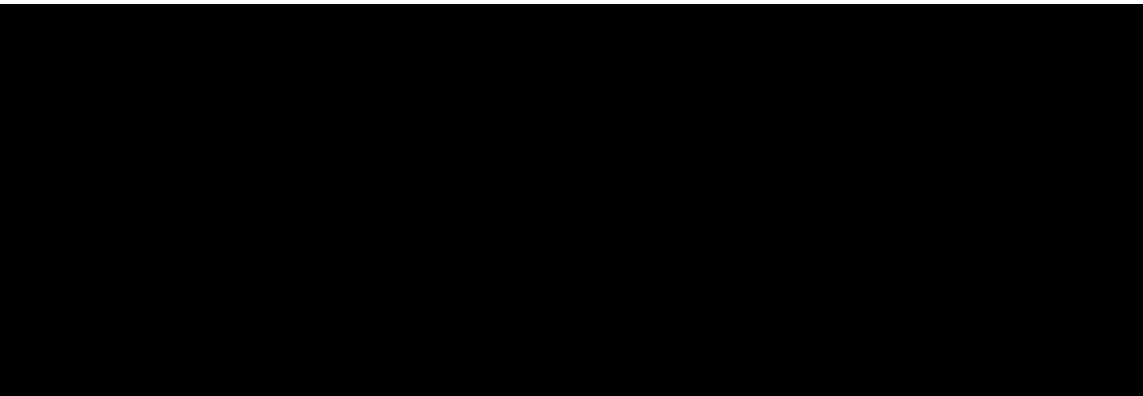
8.3.2.1 Hospital Anxiety and Depression Scale

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). The below table includes HADS Anxiety and Depression Score categorization. These categorizations are listed to support the investigator’s screening of a participant’s level of anxiety and depression, however a diagnosis of depression and assessment of the severity of depression should be made by a qualified clinician.

Table 8-1. HADS Anxiety and Depression Score Categorization

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

Stern, 2014.



8.4 Safety Assessments

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

8.4.1 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. **Participant** must be in a rested and calm state for at least 5 minutes before blood pressure assessment is conducted. The position selected for a **participant** should be the same that is used throughout the study and documented on the vital signs CRF. The temperature location selected for a **participant** 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.

8.4.2 Post-dose Monitoring and Vital Signs

Participants will be observed for 2 hours following at least the first 2 doses of investigational product on day 1 and week 2. Any **participant** 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. 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 doses. If systemic injection-related reactions are observed after the first 2 doses, the 2-hour post-dose monitoring period will remain as needed.

Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature must be measured at **least every 30 minutes during** the 2-hour post-dose monitoring period before the **participant** 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 8.4.5.

8.4.3 Electrocardiograms (ECGs)

Participant must be in supine position in a rested and calm state for at least 5 minutes before electrocardiogram (ECG) assessment is conducted. If the **participant** is unable to be in the supine position, the **participant** should be in most recumbent position as possible. The 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 **participant'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. Clinically significant changes from screening as assessed by the investigator should be recorded on the ECG eCRF and any adverse event is to be recorded as per Section 8.4.5.

8.4.4 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 **participant** represents a clinically significant change from the **participant'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).

8.4.5 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.

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

8.4.5.1.1 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 **participant** that occur after first dose of investigational product through week 52/EOT for **participants** who enroll in the long-term maintenance study (Study [REDACTED]), and through the SFU visit for **participants** 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 [REDACTED] will be monitored. **These events may require investigational product to be withheld or discontinued as detailed in Section 6.2.2: Dose Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation.**

8.4.5.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the **participant** that occur after signing of the informed consent through week 52/EOT for **participants** who enroll in the long-term maintenance study (Study [REDACTED]), and through the SFU visit for **participants** 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.

8.4.5.1.3 Adverse Event Adjudication

Potential Cardiovascular Events

In order to evaluate cardiovascular events during the study, all deaths, and serious adverse 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 pre-defined 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.

8.4.5.1.4 Serious Adverse Events After the Protocol Required Reporting Period

There is no requirement to actively monitor study **participants** after the study has ended with regards to study **participants** 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 **or designee** 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 **participant's** records after the **participant** ends the study.

8.4.5.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the **participant** is the preferred method to inquire about adverse event occurrence.

If a **participant** 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, etc) 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.

8.4.5.3 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 **participant** 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 **participant** 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 **or designee** 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.

8.4.5.4 Regulatory Reporting Requirements for Safety Information

If **participant** is permanently withdrawn from investigational product(s) and/or [REDACTED] because of a serious adverse event, this information must be submitted to Amgen **or designee**.

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 **participants** 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 for suspected unexpected serious adverse reactions (**SUSARs**) **will be reported by Amgen** according to local regulatory requirements (**eg, electronic submission to the Eudravigilance database in the EU as per EU Clinical Trial Regulation 536/2014**) as well as Amgen 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

Amgen will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report [ASR] in the EU) 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.

8.4.5.5 Safety Monitoring Plan

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

8.4.5.6 Other Safety Findings/Special Situations

All medication errors, misuse, or abuse of the investigational product when associated with a serious adverse event must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by collecting and recording the other safety findings/special situations (OSF/SS) event on the Clinical Trial electronic Serious Adverse Event (eSAE) Contingency Report Form and submitting the form to Amgen Global Patient Safety or designee.

Further details and definitions regarding OSF/SS - medication errors, misuse, or abuse, can be found in Section 11.4.

8.4.5.7 Pregnancy and Lactation

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

If a pregnancy **and/or lactation** is reported, the investigator is to inform Amgen **or designee** 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 pre-enrollment for **participants** of childbearing potential, as described in the Schedule of Activities.

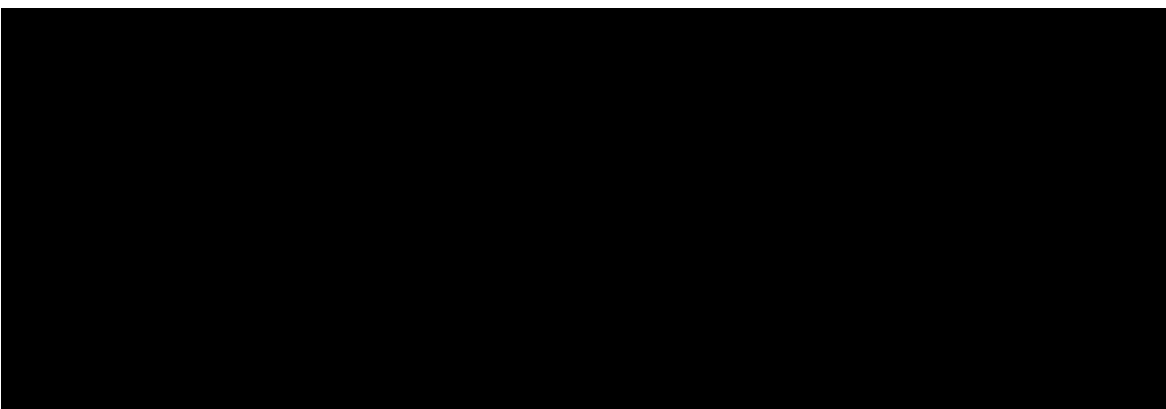
Note: **Participants** who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. If a **participant**, or the partner of a **participant assigned male at birth**, becomes pregnant it must be reported on the Pregnancy Notification Form, see [Figure 11-2](#)). **Investigator will collect lactation information on any participant who breastfeeds while taking investigational product through [REDACTED] weeks after the last dose of investigational product.**

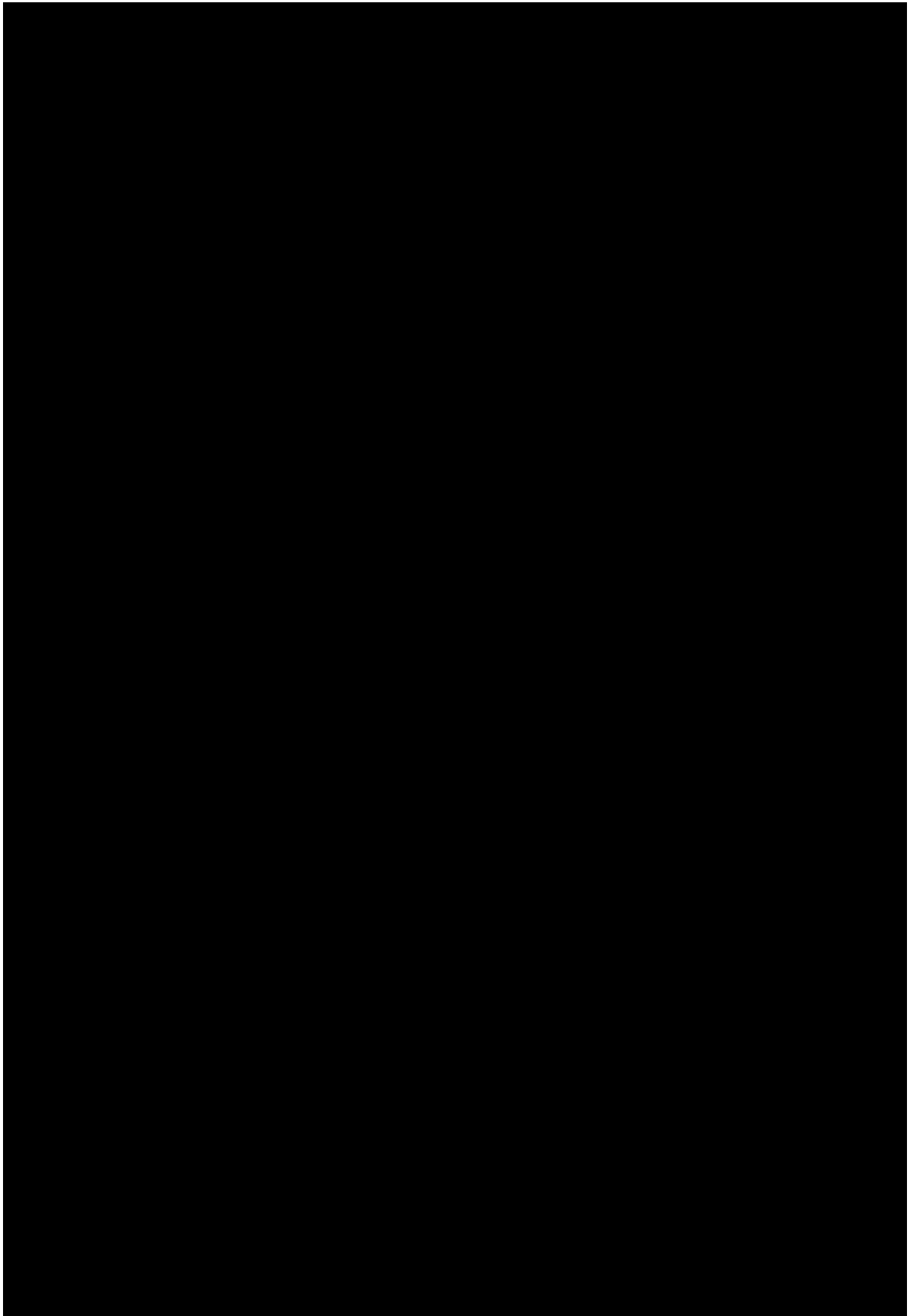
- Information will be recorded on the Lactation Notification Form (see [Section 11.5](#)) and submitted to Amgen Global Patient Safety or designee immediately and no later than 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if a participant breastfeeds during the study as described in the exclusion criteria (see [Section 5.2](#)).
- With the participant's signed consent for release of parent and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any participant who breastfeeds while taking investigational product through [REDACTED] weeks after the last dose of investigational product.

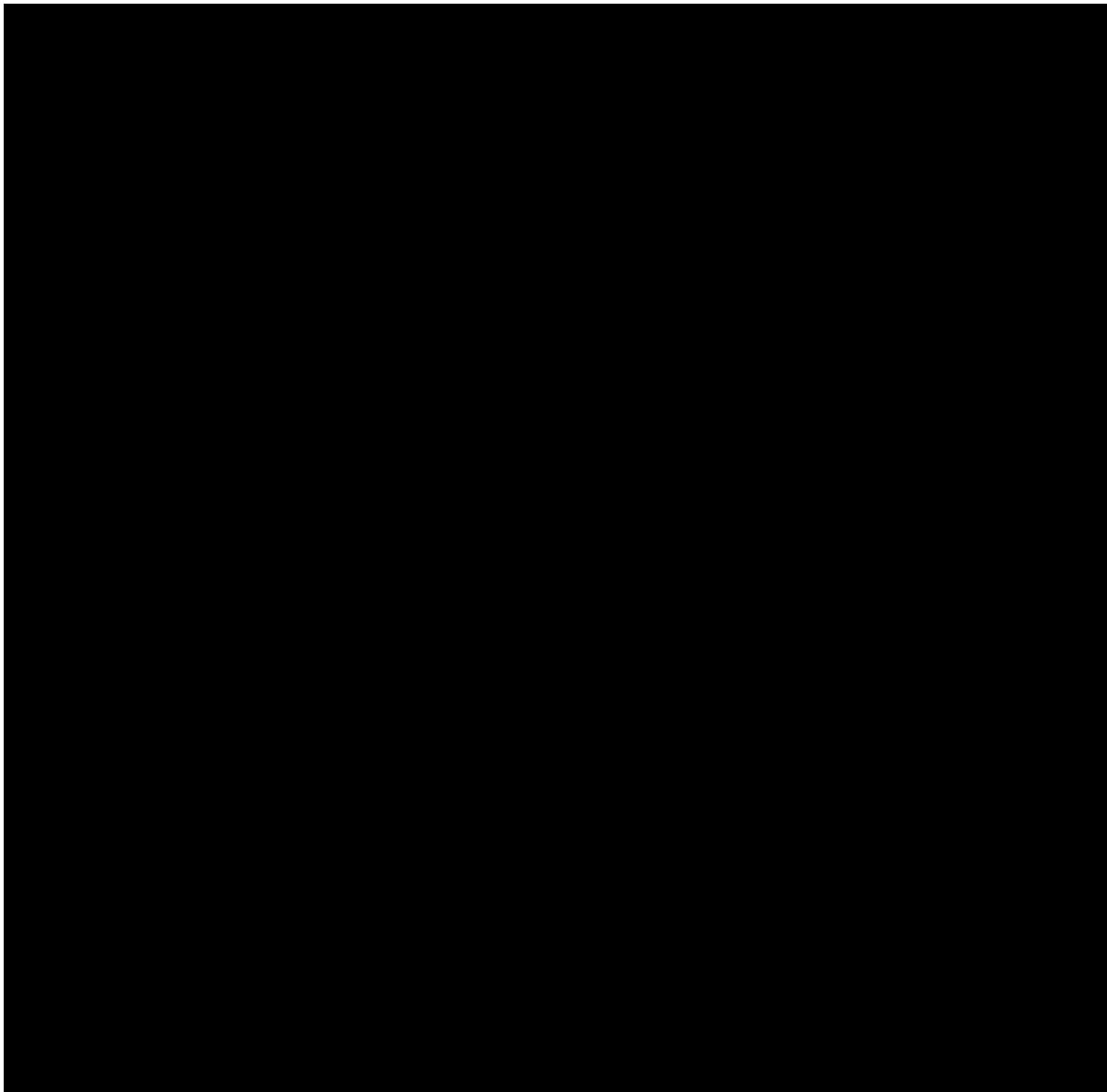
Refer to [Section 11.5](#) for contraceptive requirements.

Additional pregnancy testing should be performed Q4W during treatment with investigational product and at the safety follow-up visit when applicable, or [REDACTED] weeks after the last dose of investigational product for **participants** 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.







8.9 Other Assessments

8.9.1 Tuberculosis Testing and Tuberculosis Risk Assessment Questionnaire

Screening

All **participants** must receive QuantiFERON GOLD test from central laboratory at initial screening and Screening TB Risk Assessment Questionnaire must be completed for all **participants** as defined in the Schedule of Activities (Section 1.3). **Participants** with a positive or indeterminate QuantiFERON GOLD test are ineligible unless specific additional requirements are met (see Section 5.2). For **participants** 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 (Section 1.3) to evaluate **participants** for risks and symptoms of TB. If a **participant** 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 on-treatment 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.
- **Participants** with confirmed active TB require permanent discontinuation of the investigational product as indicated in Section 6.2.2.1.
- In case of diagnosis of latent TB during investigational product treatment, prophylaxis treatment should be initiated immediately based on the local guideline. The investigational product should not be withheld but may be interrupted per PI discretion. The **participant** should be re-evaluated for signs and symptoms of TB and for prophylactic toxicity within 4 weeks of initiation of prophylactic treatment.

If at any time point the QuantiFERON GOLD test is positive or indeterminate, the test may be repeated. If the repeated result is negative, the investigator may consider the **participant** to be negative based on the absence of symptoms and clinical judgment; if the repeat testing result is positive or indeterminate, then the **participant** 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

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

9.2 Sample Size Determination

Approximately 170 adolescent **participants** will be enrolled in the study. Assuming the dropout rate during the first 24 weeks being 10% and the subsequent 28 weeks being 20% of the remaining **participants** at week 24, it is expected that approximately 122 adolescent **participants** will be exposed to 52 weeks of rocatinlimab [REDACTED] mg.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Full Analysis Set	All participants enrolled in the study
Safety Analysis Set	All participants who receive at least 1 dose of investigational product

9.3.1 Covariates

Not applicable for primary safety endpoint.

9.3.2 Subgroups

Not applicable for primary safety endpoint.

9.4 Statistical Analyses

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

9.4.1 Planned Analyses

9.4.1.1 Primary Analysis

The primary analysis will be conducted when all **participants** have completed the week 52/EOT visit, and the data have been entered, cleaned, and locked. The objective of the analysis is to describe safety and [REDACTED] on all **participants** over the 52-week treatment period 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 **participants** have completed the EOS visit, and the data have been entered, cleaned, and locked. The objective of the final analysis is to describe complete safety data through EOS on all **participants** over the entire study period.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Participant disposition, demographics, and baseline disease characteristics will be summarized descriptively. For categorical endpoints, the descriptive statistics will contain frequency, percentage, and corresponding 95% 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
Secondary	Not applicable.
Exploratory	Will be described in the SAP finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	See Section 9.4.2.3.2

9.4.2.3.2 Adverse Events

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

9.4.2.3.3 Laboratory Test Results

The analysis of safety laboratory results will include summary statistics over time at selected time points. Shifts in grades of selected safety laboratory values between baseline and the worst on-study value will be tabulated.

9.4.2.3.4 Vital Signs

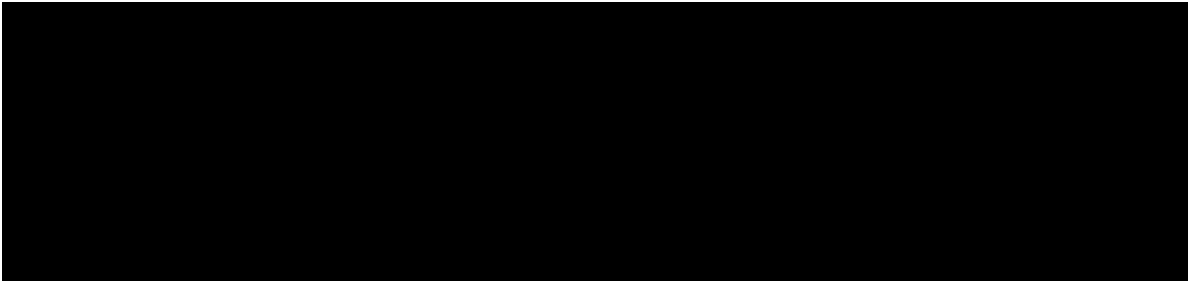
The analyses of vital signs will include summary statistics over time. Shifts in vital sign values between baseline and the worst on-study value will be tabulated.

9.4.2.3.5 Physical Measurements

The analysis of physical measurements will include summary statistics over time.

9.4.2.3.6 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 **participant** incidence of abnormal ECG diagnosis will be summarized.



9.4.2.3.8 Exposure to Investigational Product

Exposure to investigational product will be summarized. 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.

9.4.2.3.9 Exposure to Concomitant Medication

Number and percentage of **participants** receiving therapies of interest will be summarized by category.

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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
anti-HBc	anti-hepatitis B core antibody
ASR	Annual Safety Report
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BIL	bilirubin
BSA	body surface area
CFR	U.S. Code of Federal Regulations
C _{max}	maximum plasma concentration
COVID-19	coronavirus disease-19
CRF	Case Report Form
CRO	contract research organization
DILI	drug induced liver injury
DMC	data monitoring committee
DSUR	Development Safety Update Report
EASI	Eczema Area and Severity Index
EASI 50	achievement of $\geq 50\%$ reduction from baseline in EASI score
EASI 75	achievement of $\geq 75\%$ reduction from baseline in EASI score
EASI 90	achievement of $\geq 90\%$ reduction from baseline in EASI score
EASI 100	achievement of 100% reduction from baseline in EASI score
ECG	electrocardiogram
eCOA	electronic clinical outcome assessments
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMR	electronic medical record
EOS	end of study
EOT	end of treatment
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
IRT	interactive response technology
IV	intravenous
JAK	janus kinase
KS	Kaposi Sarcoma
MACE	major adverse cardiovascular event
NCT	National Clinical Trials
OX40	CD134
OX40L	OX40 Ligand
PCR	polymerase chain reaction
PDE4	phosphodiesterase type 4
PI	principal investigator
PK	pharmacokinetics
Q2W	every 2 weeks
Q4W	every 4 weeks
QTc	corrected QT interval
rIGA	revised Investigator's Global Assessment
rIGA 0/1	Achieving vIGA-AD 1 response with presence of only barely perceptible erythema or vIGA-AD 0 response
rSDR/V	remote Source Data Review and Verification
SAP	statistical analysis plan
SC	subcutaneous
SFU	safety follow-up

TB	tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
Th2	t helper type 2 cell
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
UV	ultraviolet
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis
vIGA-AD 0/1	Achieving a vIGA-AD score of 0 (clear) or 1 (almost clear) with $\geq$ 2-point reduction from baseline
vIGA-AD 0	Achieving a vIGA-AD score of 0 (clear) with $\geq$ 2-point reduction from baseline
vIGA-AD 1	Achieving a vIGA-AD score of 1 (almost clear) with $\geq$ 2-point reduction from baseline

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 **participants** 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	<u>Central Laboratory:</u>
Potassium	PTT/APTT	pH	Nucleated RBC	
Chloride		Blood	Hemoglobin	
Bicarbonate		Protein	Hematocrit	
Total protein		Glucose	MCV	
Albumin		Bilirubin	MCH	Hep B surface antigen
Calcium		WBC	MCHC	Anti-Hep B core antibody
Magnesium		RBC	RDW	Hep C antibody
Phosphorus		Epithelial cells	Reticulocytes	HIV antibody
Glucose		Bacteria	Platelets	HCV RNA
BUN (Urea)		Casts	WBC	HBV DNA
Creatinine		Crystals	Differential	QuantiFERON GOLD
Creatine Kinase			• Bands/stabs	Serum pregnancy test
Uric acid			• Segmented Neutrophils	
Total bilirubin			• Total Neutrophils	
Direct bilirubin			• Eosinophils	
ALP			• Basophils	
LDH			• Lymphocytes	
AST (SGOT)			• Monocytes	
ALT (SGPT)				<u>Local Laboratory:</u>
Lipids (Cholesterol, HDL, LDL, Triglycerides)				Urine
eGFR				Pregnancy test

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate as determined by the bedside Schwartz equation; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; 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; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

If the **participant** 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. Potential DILI 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

An Independent Biostatistics Group (IBG) will perform the analysis and generate the data monitoring committee (DMC) report. The DMC will review all available safety data periodically and consider efficacy data in order to assess the risk/benefit profile of rocatinlimab. The IBG and DMC will have access to **participants'** individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC and IBG will not have any direct contact with study site personnel or **participants**. 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 (IB), and other relevant documents (eg, **participant** recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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 **participants** 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 U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

A copy of the protocol, proposed ICF and assent form, other written **participant** information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of **participants** into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for 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.

Informed Consent Process

An initial sample informed consent/assent form is provided for the investigator to prepare the informed consent/assent document to be used at his or her site. Updates to the

sample informed consent/assent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent/assent 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 **participant**, or his/her legally authorized representative (if allowed, depending on the country concerned), 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.

Participants must be informed that their participation is voluntary. **Participants** or their legally authorized representative (if allowed, depending on the country concerned) defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective **participant**, to the **participant'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 **participant** 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 **participant** if the **participant** has a primary care physician and if the **participant** agrees to have his/her primary care physician informed of the **participant's** participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the **participant** agrees to such notification, the investigator is to inform the **participant's** primary care physician of the **participant's** participation in the clinical study. If the **participant** does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the **participant's** medical record.

The acquisition of informed consent and the **participant's** legally acceptable representative's (if allowed, depending on the country concerned) agreement or refusal of his/her notification of the primary care physician is to be documented in the **participant's** medical records, and the informed consent form is to be signed and personally dated by the **participant** or a legally authorized representative (if allowed,

depending on the country concerned) and by the person who conducted the informed consent discussion. **Participant** withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the **participant's** medical records; refer to Section 7.

Participants must be re-consented/assented to the most current version of the informed consent form(s) during their participation in the study.

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 **participant** or the **participant's** legally authorized representative (if allowed, depending on the country concerned).

A **participant** who is rescreened is not required to sign another informed consent/assent form if the rescreening occurs within 30 days from the previous informed consent/assent form signature date.

The informed consent form (ICF) or assent 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 **participant** the objectives of the future research. **Participants** 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 **participant's** agreement to allow any remaining specimens to be used for future research. **Participants** who decline to participate will not provide this separate signature.

Data Protection/Participant Confidentiality

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

The **participant** will be assigned a unique identifier by the sponsor. Any **participant** records or datasets that are transferred to the sponsor will contain the identifier only; **participant** names or any information which would make the **participant** 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, **participants** 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.

Participant data should be kept in a secure location. Access to **participant** 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 **participant'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 **participant** 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 **participant** confidentiality and privacy.

Participants are designated by a unique subject identification number in the sponsor's systems. The sponsor uses access-controlled systems to house, review and analyze **participant** data. These systems are backed-up regularly to minimize the risk of loss of **participant** 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 **participant** 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.

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 **participants**

Data Quality Assurance

All **participant** 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 in 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.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of **participants** 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 **participant** 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 Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, investigational product(s) and/or [REDACTED] 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.

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 **participants** 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 **participant** 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 **participant'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 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:

- **Participant** files containing completed CRFs, informed consent forms, and **participant** identification list
- Study files containing the protocol with all amendments, IB, 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] 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 study. 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.

Participants 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 **participants** 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.

Results Reporting

Results will be reported to clinical trial registries in accordance with the applicable regulatory requirements. The final summary results will be reported following the global end of study (as defined in Section 4.4) to ensure data from all sites globally are included in the reported results.

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 participant 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 intentional overdose of either study treatment or a concomitant medication. Intentional overdose will be reported as an adverse event/serious adverse event when it is taken with possible suicidal/self-harming intent. Such intentional overdoses are to be reported regardless of sequelae on the Events CRF. Accidental/unintentional overdose will be captured as a Medication Error. “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 **participant** 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 **participant** 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 **participant** 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.

Other Safety Findings/Special Situations: Medication Errors, Misuse or Abuse

All medication errors, misuse or abuse of the investigational product when associated with a serious adverse event, the OSF/SS must be reported to Amgen or designee immediately and no later than 24 hours of the investigator's awareness by submitting the paper-based Clinical Trial eSAE Contingency Report Form.

Definitions	Medication Error: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the participant (eg, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice).
	Misuse: A misuse refers to situations where the medicinal product, combination product, or medical device is intentionally and inappropriately used not in accordance or outside what is foreseen in the protocol.
	Abuse: An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, combination product, or medical device, which is accompanied by harmful physical or psychological effects.

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 Event Case Report Form (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;
 - **Assessment of relatedness to study-required activity and/or procedures is only required for serious adverse events;**
 - 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 **participant's** medical records to sponsor/responsible contract research organization (CRO) in lieu of completion of the Events CRF page.
- 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 **participant** identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen or delegated party (if applicable).
- 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(s) and each occurrence of each adverse event/serious adverse event. The investigator is obligated to assess the relationship between investigational product, [REDACTED], device, study-required activity and/or procedure(s), and each occurrence of each 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 (IB) 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 he/she has 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 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 **participant** is permanently withdrawn from investigational product(s) and/or [REDACTED] because of a serious adverse event, this information must be submitted to Amgen.
- If a **participant** 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 electronic data capture (EDC) system.
- If the EDC system is unavailable, then the site will report the information to Amgen using a paper-based **Clinical Trial Serious Adverse Event Contingency Report Form** (also referred to as the **Clinical Trial eSAE Contingency Report Form**) (see [Figure 11-1](#)) immediately and no later than 24 hours of the investigator's awareness of the event.
- **The primary mechanism for the site to report the Other Safety Finding/Special Situation associated with a serious adverse event to Amgen is by submitting the Clinical Trial eSAE Contingency Report Form 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 **participant** 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 **Clinical Trial** 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 immediately and no later than 24 hours following the investigator's awareness of the event. The investigator should use the paper-based **Clinical Trial** Serious Adverse Event Contingency Report Form to report the event.

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

AMGEN® Study # 20210263 AMG 451		Clinical Trial Electronic Serious Adverse Event Contingency Report Form <u>For Restricted Use</u>			
<u>Notify Amgen Immediately and no later than 24 Hours of awareness of the serious adverse event/other safety finding/special situation</u>					
Reason for reporting this event using the Serious Adverse Event Contingency Report Form:					
The Clinical Trial Database (eg, Rave): ☐ Is not available due to internet outage at my study site ☐ Is not yet available for this study ☐ Has been closed for this study ☐ Other Safety Finding/Special Situation associated with a Serious Adverse Event					
If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the serious adverse event term: _____ and start date: Day _____ Month _____ Year _____					
<<Amgen Safety Fax Number to be populated by the Study Manager/Protocol Author/designee prior to providing to sites: SELECT OR TYPE IN A FAX#>> If an email address or eFax is used, the Primary Study Team (e.g., Clinical Manager or Delegate) will need to ensure secure email exchange is established between the Provider/Study Sites, Vendor/Supplier, Study Sites and Amgen.					
1. SITE INFORMATION					
Site Number 		Investigator 		Country 	
Reporter 		Phone Number ()		Fax Number ()	
2. PARTICIPANT INFORMATION					
Participant ID Number 		Age at event onset 		Sex ☐ F ☐ M	
Race 		If applicable, provide End of Study date 			
3. SERIOUS ADVERSE EVENT or Other Safety Finding/Special Situation associated with a 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 OR Other Safety Finding/Special Situation associated with a Serious Adverse Event List one event per line.		Date Started Day Month Year 		Date Ended Day Month Year 	
Check only if event occurred before first dose of IP		Is event serious? ☐ Yes ☐ No		Relationship Is there a reasonable possibility that the Event may have been caused by IP or the investigational medical device? Rocatinlimab <Device> <Device> <Device> No/Yes No/Yes No/Yes No/Yes	
Outcome of Event Resolved Not resolved Fatal Unknown		Check only if event is related to study procedure eg, biopsy			
Serious Criteria: 01 Fatal 02 Immediately life-threatening		03 Required hospitalization or prolonged hospitalization 04 Persistent or significant disability/incapacity		05 Congenital anomaly / birth defect 06 Other medically important serious event	
4. Was participant 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 		

 Study # 20210263 AMG 451	Clinical Trial Electronic Serious Adverse Event Contingency Report Form For Restricted Use
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		Site Number				Participant ID Number																			
5. Was IP/drug under study administered/taken prior to this event? ☐ No ☐ Yes If yes, please complete all of Section 5																									
IP/ Device:		Date of Initial Dose				Prior to, or at time of Event Date of Dose				Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld				Lot # and Serial #								
		Day	Month	Year		Day	Month	Year																	
Rocatinlimab																	Lot #: _____ ☐ Unknown Serial #: _____ ☐ Unavailable / Unknown								
<<IP/Device>>																	Lot #: _____ ☐ Unknown Serial #: _____ ☐ Unavailable / Unknown								
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:																									
Medication Name(s)		Start Date			Stop Date			Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med										
		Day	Month	Year	Day	Month	Year	No✓	Yes✓	No✓	Yes✓				No✓	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	Test																								
	Unit																								
Day	Month	Year																							
9. OTHER RELEVANT TESTS (diagnostics and procedures) Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:																									
Date		Additional Tests										Results						Units							
Day	Month	Year																							

[illegible]

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

Study-specific contraception requirements for **participants assigned female at birth of childbearing potential** who have reached puberty are outlined in Section 5.2.

Contraceptive use and methods should be consistent with local regulations for **participants** participating in clinical studies.

Participants assigned female at birth 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 ■ weeks after the last dose of investigational product.

Definition of Childbearing Potential

A **participant** is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Participants 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 **participant's** medical records; 2) **participant's** medical examination; or 3) **participant's** medical history interview.

Contraception Methods for Participants Assigned Female at Birth

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Vasectomized partner (provided that partner is the sole sexual partner of the **participant** 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 **participant**)

Collection of Pregnancy Information

Participants Who Become Pregnant

- Investigator will collect pregnancy information on any **participant** who becomes pregnant while taking investigational product through █ weeks after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form (see [Figure 11-2](#)). The form must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of a **participant'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 **participant'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 participant who becomes pregnant while taking investigational product through █ weeks after the last dose of the study drug. 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 **participants**, they may learn of a serious adverse event through spontaneous reporting.
- Any **participant** who becomes pregnant while participating will discontinue study treatment while pregnant (see [Section 7.1](#) for details).

Participants With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- Participants **assigned male at birth** are not required to use forms of contraception during treatment with rocatinlimab. However, **these** participants should let their partner know they are in this study.
- In the event a **participant's partner becomes pregnant** during treatment, and for an additional weeks after the last dose of the investigational product, the information will be recorded on the Pregnancy Notification Form. The form (see [Figure 11-2](#)) 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 partner to obtain additional pregnancy information.
- After obtaining the **pregnant** 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 **participant** who breastfeeds while taking investigational product through [REDACTED] weeks after last dose of investigational product.
- 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 **a participant** breastfeeds during the study as described in exclusion criterion [224](#).
- With the **participant's** signed consent for release of **parent** and infant health information, the investigator will collect **parent** and infant health information and complete the lactation questionnaire on any **participant** who breastfeeds while taking investigational product through [REDACTED] weeks after discontinuing investigational product.

Figure 11-2. 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: 20210263

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 ____ / ~~yyy~~ ____

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

If yes, provide product (or study drug) stop date: mm ____ / dd ____ / ~~yyy~~ ____

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

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm ____ / dd ____ / ~~yyy~~ ____ ☐ Unknown ☐ N/A

Estimated date of delivery mm ____ / dd ____ / ~~yyy~~ ____

If N/A, date of termination (actual or planned) mm ____ / dd ____ / ~~yyy~~ ____

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

If yes, provide date of delivery: mm ____ / dd ____ / ~~yyy~~ ____

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: _____

Amgen Proprietary - Confidential

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: 20210263

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

Any blood, [REDACTED], or [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 **participants**. 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.

If informed consent/assent is provided by the **participant's** legally acceptable representative (if allowed, depending on the country concerned), 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, 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 **participant** directly or to alter the treatment course, the results of [REDACTED] or other [REDACTED] studies are not placed in the **participant's** medical record and are not to be made available to the **participant**, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The **participant** and/or the **participant's** legally acceptable representative (if allowed, depending on the country concerned) retain the right to request that the sample material be destroyed by contacting the investigator. Following the request from the **participant** and/or the **participant's** legally acceptable representative (if allowed, depending on the country concerned), 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 shall be destroyed immediately (ie, as soon as possible) after withdrawal request for destruction. However, information collected from samples prior to the withdrawal 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 **participant** 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 **participant** 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 **participant** confidentiality.

11.7 Appendix 7. Hepatotoxicity [REDACTED]: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Participants 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 [REDACTED], 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 [REDACTED] Due to Potential Hepatotoxicity.

The following [REDACTED] and/or withholding rules apply to **participants** 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 **participant** 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 [REDACTED] Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
INR	--	OR > 1.5 (for participants not on anticoagulation therapy)
AST/ALT	OR > 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)	AND > 3x ULN (when baseline was < ULN) in the presence of no important alternative causes for elevated AST/ALT and/or TBL values
ALP	OR > 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 [REDACTED]

[REDACTED] After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then investigational product is to be permanently discontinued. **Participants** 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 case report form (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 **participants** in whom investigational product(s) [REDACTED] [REDACTED] is/are withheld (either permanently or conditionally) due to potential DILI as specified in [Table 11-3](#) or who experience AST or ALT elevations $> 3 \times$ upper limit of normal (ULN) or 2-fold increases above baseline values for **participants** with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the **participant’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 $> 2 \times$ 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 and/or [REDACTED]

[REDACTED] has/have been discontinued AND the **participant** 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 (Ig)G, 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 **participant** 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/or [REDACTED]. 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

Potency Category	Classification	Medication Name / Formulation / Strength
Low	VII	- Dexamethasone cream 0.1% - Hydrocortisone cream/lotion/ointment/solution 0.25%, 0.5%, 1.0%, 2.5% - Hydrocortisone acetate cream 0.5%, 1.0% - Methylprednisolone acetate cream 0.25%
	VI	- Alclometasone dipropionate cream/ointment/lotion 0.05% - Betamethasone valerate cream/lotion 0.05% - Betamethasone valerate lotion 0.1% - Desonide cream/lotion/gel/foam/ointment 0.05% - Fluocinolone acetonide cream/solution 0.01%
Medium	V	- Betamethasone dipropionate lotion 0.02% - Betamethasone benzoate cream/lotion 0.025% - Betamethasone valerate cream/foam/ointment 0.1% - Betamethasone valerate foam 0.12% - Fluocinolone acetonide cream 0.025% - Flurandrenolide (Fludroxycortide) cream 0.025%, 0.05% - Hydrocortisone butyrate cream 0.1% - Hydrocortisone probutate cream 0.1% - Hydrocortisone valerate cream 0.2% - Prednicarbate cream 0.1% - Triamcinolone acetonide lotion 0.1%
	IV	- Betamethasone benzoate gel 0.025% - Clocortolone pivalate cream 0.1% - Fluocinolone acetonide ointment 0.025% - Flurandrenolide (Fludroxycortide) ointment 0.05% - Desoximetasone cream 0.05% - Fluticasone propionate lotion 0.05% - Hydrocortisone valerate ointment 0.2% - Mometasone furoate cream 0.1% - Triamcinolone acetonide cream/ointment/spray 0.1%
High	III	- Diflorasone diacetate cream 0.05% - Diflucortolone valerate ointment 0.1% - Fluocinonide cream 0.05%
	II	- Amcinonide cream/lotion/ointment 0.1% - Betamethasone dipropionate cream/foam/ointment/solution 0.05% - Desoximetasone cream/ointment 0.25% - Desoximetasone gel 0.05% - Fluocinonide ointment/gel/solution 0.05% - Halcinonide cream/ointment 0.1% - Mometasone furoate ointment 0.1% - Triamcinolone acetonide cream/ointment 0.5%
Super-high	I	- Augmented betamethasone dipropionate gel/ointment 0.05% - Clobetasol propionate lotion/cream/solution/foam/ointment 0.05% - Flurandrenolide (Fludroxycortide) tape 4mcg/sq.cm - Halobetasol propionate cream/lotion/ointment 0.05% - Diflorasone diacetate ointment 0.05%

Note: This list is provided for reference only. There may be other topical corticosteroids not included here. To determine the potency category of other topical corticosteroids, please consult published regulatory or reference materials, or contact the medical monitor.

Source: World Health Organization [WHO]. Model Prescribing Information: Drugs used in skin diseases. 1997; Geneva.

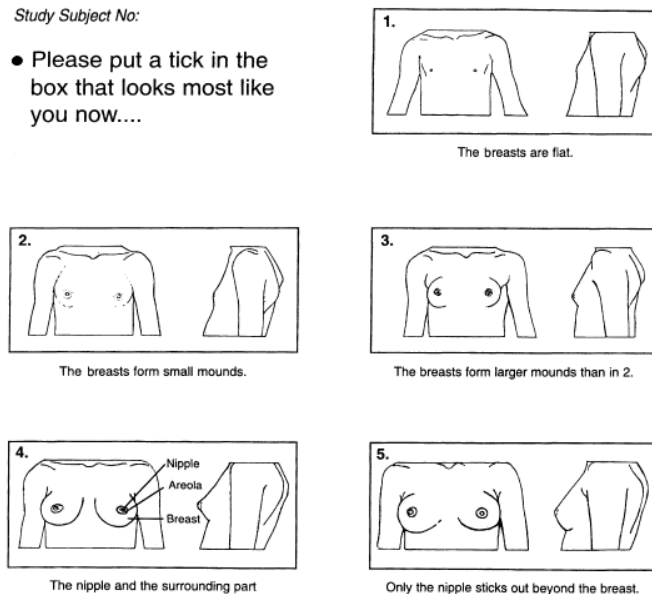
Tadicherla S, Ross K, Shenefelt PD, Fenske NA. Topical corticosteroids in dermatology. *J Drugs Dermatol*. 2009;8(12):1093-1105.

11.9 Appendix 9. Pubertal Maturation Self-assessment (Tanner Staging) Scale

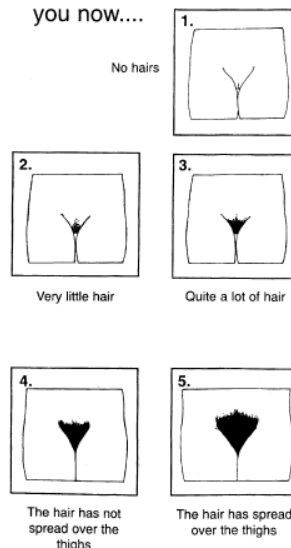
Female Tanner Staging (Sample)

Study Subject No:

- Please put a tick in the box that looks most like you now....



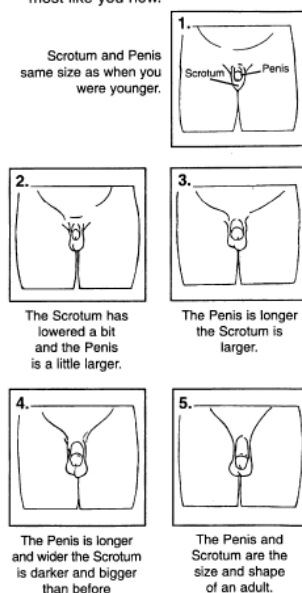
- Please put a tick in the box that looks most like you now....



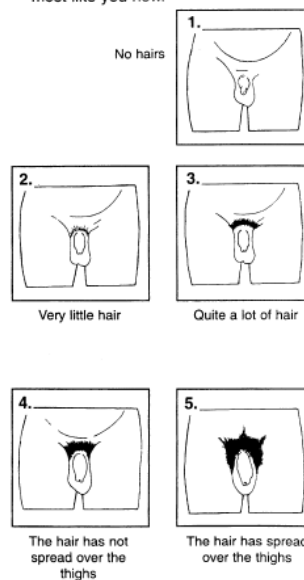
Male Tanner Staging (Sample)

Study Subject No:

- Please look at the **Penis and Scrotum** only in these pictures.
- Please put a tick in the box that looks most like you now.



- Please look at the **Pubic Hair** only in these pictures.
- Please put a tick in the box that looks most like you now.



Source: Taylor SJ, Whincup PH, Hindmarsh PC, Lampe F, Odoki K, Cook DG. Performance of a new pubertal self-assessment questionnaire: a preliminary study. *Paediatric and Perinatal Epidemiology*. 2001;15:88-94.



Approval Signatures

Document Name: Protocol Amendment rocatinlimab 20210263 4

Document Description: AMG 451 20210263 Protocol Amendment 4

Document Number: CLIN-000287236

Approval Date: 18 Sep 2024

Type of Study Protocol: Amendment

Protocol Amendment No.: 4

Document Approvals	
Reason for Signing: Management	Name: [REDACTED] Date of Signature: 18-Sep-2024 01:06:29 GMT+0000

Amendment 3

Protocol Title: A Phase 3, Open-label, 52-week Study to Assess the Safety, Tolerability, and Efficacy of Rocatinlimab (AMG 451) in Adolescent Subjects Aged ≥ 12 to < 18 years With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit)

Amgen Protocol Number: Rocatinlimab 20210263

EU CT Number: 2022-501535-16

NCT Number: NCT05633355

Amendment Date: 08 December 2023

Rationale:

This protocol has been amended primarily to add a protocol-defined [REDACTED] for subjects who do not demonstrate an adequate benefit after 36 weeks of treatment with the investigational product and to add that subjects may continue treatment with the investigational product if the specified criteria are met as outlined in Section 6.2.2.1 of the protocol. Other changes to the protocol are specified below:

- Update to the Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD), Eczema Area and Severity Index (EASI), and Investigational Product Administration Schedule of Activities; Section 1.3, to include footnotes for clarity on the [REDACTED] and applicable criteria.
- Update to section 4.1 to describe the protocol defined [REDACTED] and outline the criteria under which a subject may continue investigational product treatment.
- Update to table 6-1; Investigational Products to state that investigational product sequential doses should not be given less than 8 days apart.
- Update to table 11-4; Topical Corticosteroids Potency Category to move betamethasone valerate foam/ointment 0.1% and betamethasone valerate foam 0.12% from the high classification category III to the medium classification, category V. Discrepancies existed between the potency table from the 20210263 study and the other AMG 451 atopic dermatitis study potency tables, as well as published guidelines on the potency of various TCS. The changes were made to align potency tables across studies as well as with published potency tables.

- Update editorial changes, including administrative, abbreviations, typographical, and formatting corrections throughout the protocol.

Amendment 2

Protocol Title: A Phase 3, Open-label, 52-week Study to Assess the Safety, Tolerability, and Efficacy of Rocatinlimab (AMG 451) in Adolescent Subjects Aged ≥ 12 to < 18 years With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit)

Amgen Protocol Number (Rocatinlimab [AMG 451]) 20210263

EU CT number: 2022-501535-16

NCT number: NCT05633355

Amendment Date (amendment 2): 23 May 2023

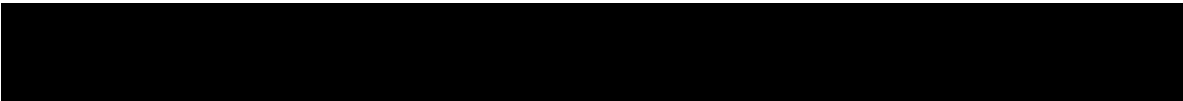
Amendment Date (Superseding amendment 2): 13 June 2023

Rationale:

On 13 June 2023, the protocol amendment 2 was superseded to remove inclusion criterion 113 and add statement regarding the psychiatric treatment regimen in exclusion criteria.

Protocol amendment 2 is being updated to address feedback received from the regulatory agencies. The following changes have been implemented to:

- Update the Schedule of Activities (SoA) table to:
 - Add Screening TB risk assessment questionnaire at day 1 pre-enrollment and on-study TB risk assessment questionnaire at unscheduled visit.
 - Add laboratory assessments (coagulation, human immunodeficiency virus (HIV), Hepatitis B and C, QuantiFERON GOLD, [REDACTED], [REDACTED], [REDACTED], hepatitis B DNA, serum pregnancy, urinalysis, and electrocardiogram (ECG) at unscheduled visits.
 - Remove the “Per Investigator Discretion” from Urinalysis.
 - Add a new row for ‘Mental health randomization review’.
 - Update visits for concomitant therapies review.

- Add that a 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.
 - Clarify that the unscheduled visits may occur at any time point during the treatment period, and only those laboratory assessments and/or efficacy/clinical outcome assessments deemed necessary should be performed at unscheduled visits at the discretion of the investigator.
- Update the Benefit/Risk Assessment
- Update inclusion criteria to specify that subjects with previous systemic treatment for atopic dermatitis (AD) are also considered as inadequate responders to topical treatments and are potentially eligible to be included in the study after appropriate washout.
- Update exclusion criteria to:
 - Clarify that a positive or indeterminate QuantiFERON test is allowed if certain exceptions are present at day 1 pre-enrollment per Screening tuberculosis (TB) Risk Assessment Questionnaire provided by Amgen.
 - Remove the exclusion criterion ‘anti-pruritic agents (eg, crotamiton) or antihistamines used for treatment of pruritus’.
 - Clarify to indicate the following: currently receiving treatment in another investigational device or drug study, or less than ■ days (■ weeks for Japan) or 5 half-lives, whichever is longer, since ending treatment on another investigational device or drug study(ies) prior to day 1 prandomization. Other investigational procedures while participating in this study are excluded.
- Clarify that an individual subject is considered to have completed the study if they have completed the last scheduled visit shown in the SoA table and that the maximum total study duration for an individual subject is approximately 68 weeks.
- Update the guidance for certain therapeutics for non-AD related conditions, including prohibited therapies (Table 6-2).
- Update the guidance for rescue therapy for AD (Table 6-3).
- 

- [REDACTED]
- Update the general assessment 'Mental Health Assessment'.
- Update the general assessment 'Hospital Anxiety and Depression Scale (HADS)' to include HADS Anxiety and Depression categorization scores (Table 8-1).
- Update the safety assessment 'Clinical Laboratory Assessments' for alignment with other studies.
- Specify that the adverse events of special interest will be monitored.
- Inform that the use of prohibited rescue therapies may require permanent discontinuation or temporary interruption of investigational product.
- Update contraceptive guidance for male subjects whose partner was pregnant at the time of beginning of the study or if the female partner becomes pregnant at any time while the male participant is on-study.
- Update that 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.
- Update permanent discontinuation language for neutropenia following an adverse event.
- Make administrative and editorial changes throughout the protocol for clarification and consistency.

Amendment 2

Protocol Title: A Phase 3, Open-label, 52-week Study to Assess the Safety, Tolerability, and Efficacy of Rocatinlimab (AMG 451) in Adolescent Subjects Aged ≥ 12 to < 18 years With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Orbit)

Amgen Protocol Number (Rocatinlimab [AMG 451]) 20210263

EU CT number: 2022-501535-16

NCT number: NCT05633355

Amendment Date: 23 May 2023

Rationale:

Protocol amendment 2 is being updated to address feedback received from the regulatory agencies. The following changes have been implemented to:

- Update the Schedule of Activities (SoA) table to:
 - Add Screening TB risk assessment questionnaire at day 1 pre-enrollment and on-study TB risk assessment questionnaire at unscheduled visit.
 - Add laboratory assessments (coagulation, human immunodeficiency virus (HIV), Hepatitis B and C, QuantiFERON GOLD, [REDACTED], [REDACTED], hepatitis B DNA, serum pregnancy, urinalysis, and electrocardiogram (ECG) at unscheduled visits.
 - Remove the “Per Investigator Discretion” from Urinalysis.
 - Add a new row for ‘Mental health randomization review’.
 - Update visits for concomitant therapies review.
 - Add that a 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.

- Clarify that the unscheduled visits may occur at any time point during the treatment period, and only those laboratory assessments and/or efficacy/clinical outcome assessments deemed necessary should be performed at unscheduled visits at the discretion of the investigator.
- Update the Benefit/Risk Assessment
- Update inclusion criteria to specify that subjects with previous systemic treatment for atopic dermatitis (AD) are also considered as inadequate responders to topical treatments and are potentially eligible to be included in the study after appropriate washout.
- Update exclusion criteria to:
 - Clarify that a positive or indeterminate QuantiFERON test is allowed if certain exceptions are present at day 1 pre-enrollment per Screening tuberculosis (TB) Risk Assessment Questionnaire provided by Amgen.
 - Remove the exclusion criterion ‘anti-pruritic agents (eg, crotamiton) or antihistamines used for treatment of pruritus’.
 - Clarify to indicate the following: currently receiving treatment in another investigational device or drug study, or less than ■ days (■ weeks for Japan) or 5 half-lives, whichever is longer, 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.
- Clarify that an individual subject is considered to have completed the study if they have completed the last scheduled visit shown in the SoA table and that the maximum total study duration for an individual subject is approximately 68 weeks.
- Update the guidance for certain therapeutics for non-AD related conditions, including prohibited therapies (Table 6-2).
- Update the guidance for rescue therapy for AD (Table 6-3).
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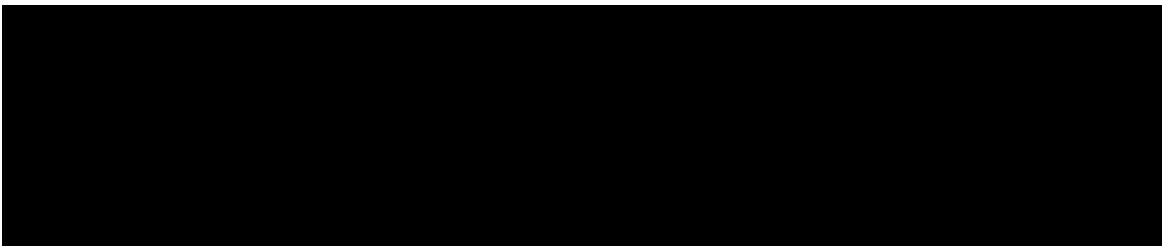
- [REDACTED]
- Update the general assessment 'Mental Health Assessment'.
- Update the general assessment 'Hospital Anxiety and Depression Scale (HADS)' to include HADS Anxiety and Depression categorization scores (Table 8-1).
- Update the safety assessment 'Clinical Laboratory Assessments' for alignment with other studies.
- Specify that the adverse events of special interest will be monitored.
- Inform that the use of prohibited rescue therapies may require permanent discontinuation or temporary interruption of investigational product.
- Update contraceptive guidance for male subjects whose partner was pregnant at the time of beginning of the study or if the female partner becomes pregnant at any time while the male participant is on-study.
- Update that 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.
- Update permanent discontinuation language for neutropenia following an adverse event.
- Make administrative and editorial changes throughout the protocol for clarification and consistency

Protocol Title: A Phase 3, Open-label, 52-week Study to Assess the Safety, Tolerability, and Efficacy of Rocatinlimab (AMG 451) in Adolescent Subjects Aged ≥ 12 to < 18 years With Moderate to severe Atopic Dermatitis (AD) (ROCKET-Orbit)

NCT Number: NCT05633355

Amendment Date: 17 February 2023

- To clarify that the study is designed to provide supportive evidence of the safety, tolerability, and efficacy of rocatinlimab in the adolescent population.
- To remove the assessment of secondary objectives and endpoints describing the efficacy of rocatinlimab [REDACTED] mg at week 24 as the [REDACTED] are for the entire duration of study.
- To update the exploratory endpoint describing the [REDACTED]
[REDACTED] || [REDACTED]
[REDACTED]
- To clarify that the subjects who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 52 for the evaluation of endpoints.
- To update text regarding eligibility for the long-term maintenance study (Study [REDACTED]) enrollment.

- To update the Schedule of Activities (SoA) table:
 - To add pubertal maturation self-assessment (Tanner Staging) at day 1, week 24, and week 52/End of Treatment (EOT).
 - To add footnote k to clarify only subjects who have not reached Tanner Stage 5 need to be further assessed according to Schedule of Activities or until reaching Tanner Stage 5, whichever comes first.
 - To add an additional visit at week 2 for 2-hour post-dose monitoring vital signs.
 - To add an additional as needed visit at week 4 through 48 for 2-hour post-dose monitoring vital signs.
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 - To update footnote v that vital signs must be measured only at the end of the 2-hour post-dose monitoring period before subject is discharged.
- To update the exclusion criteria:
 - To revise the exclusion criteria regarding subjects receiving psychiatric treatment regimen as it was already presented in inclusion criteria.
 - To remove topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), anti-pruritic agents (eg, crotamiton), or antihistamines used for treatment of pruritus from the list of agents excluded within 1 week before day 1 pre-enrollment.
 - To clarify that the other topical immunosuppressive agents do not include TCS/TCI.
 - To specify the potency of corticosteroid components in combination topical agents and to remove calcineurin inhibiting components.
- To clarify that topical and systemic rescue therapies for atopic dermatitis (AD) are discouraged during the study, but still permitted for use.
- To update that the use of antihistamines for treatment of pruritus is discouraged at any time during the study, but subjects may continue investigational product if there is the concurrent use of these therapies.
- To clarify that a washout period of 4 weeks is required for high- to super-high potency TCS prior to day 1 visit.
- To remove the minimum duration of treatment with investigational product required in the event of worsening and/or unacceptable symptoms of AD to rescue with standard of care.
- To clarify that the monitoring of mental health is necessary during screening and on-study.

- To update that subjects will be observed for 2 hours following at least the first 2 doses of investigational product on day 1 and week 2, and that 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 doses. If systemic injection-related reactions are observed after the first 2 doses, the 2-hour post-dose monitoring period will remain as needed.
- To clarify that the vital signs are measured at the end of the 2-hour post-dose monitoring period, also as and when needed from week 4 to week 48.
- To recommend the immediate prophylactic treatment in case of diagnosis of latent tuberculosis (TB) during investigational product treatment and clarify that the investigational product should not be withheld but may be interrupted per principal investigator discretion.
- To update contraceptive guidance:
 - To remove bilateral tubal ligation/occlusion as a highly effective contraceptive method.
 - To update contraception methods for female subjects to highly effective contraceptive methods.
 - To update that male participants are not required to use contraception during treatment with the investigational product, but they should let their female partner know that they are in this study.
- To update statistical planned analyses:
 - That the objective of the primary analysis is to describe safety and [REDACTED] on all subjects over the 52-week treatment period and additional safety data available during safety follow-up as of the data cutoff date.
 - That the objective of the final analysis is to describe complete safety data through the end of study on all subjects over the entire study period.
- To clarify that the estimated glomerular filtration rate (eGFR) is determined by the bedside Schwartz equation.
- To add an additional appendix “Pubertal Maturation Self-assessment (Tanner Staging) Scale” for female and male subjects.
- To add the National Clinical Trial Number NCT05633355 and correct the European Union Clinical Trial Number to remove “00”.
- To make editorial changes, including administrative, typographical, grammatical, formatting, and abbreviations, throughout the document.