## Title Page

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|---|---|---|
| **Protocol Title:** | | A Phase 3, Randomized, 24-week, Placebo-controlled, Double-blind Study to Assess the Efficacy, Safety and Tolerability of Rocatinlimab (AMG 451) Monotherapy in Adult Subjects With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Horizon) |
| **Short Protocol Title:** | | A Phase 3, Placebo-controlled, Double-blind Study Assessing Rocatinlimab (AMG 451) Monotherapy in Moderate-to-severe AD (ROCKET-Horizon) |
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| | **Address:** | One Amgen Center Drive<br>Thousand Oaks, CA, 91320 |
| | **Telephone Number:** | +1 805-447-1000 |
| **Protocol Approver** | **Name:** | [redacted], MD, MBA |
| | **Function:** | VP Global Development |
| **Key Sponsor Contact** | **Name:** | [redacted], MD |
| | **Address:** | One Amgen Center Drive<br>Thousand Oaks, CA, 91320-1799 |
| | **Telephone Number:** | [redacted] |
| | **Email Address:** | |
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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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I have read the attached protocol entitled A Phase 3, Randomized, 24-week, Placebo-controlled, Double-blind Study to Assess the Efficacy, Safety and Tolerability of Rocatinlimab (AMG 451) Monotherapy in Adult Subjects With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Horizon), dated **29 November 2023**, and agree to abide by all provisions set forth therein.

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Name of Investigator Date (DD Month YYYY)

_____
Title and Role of Investigator

_____
Institution Name

_____
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# 1. Protocol Summary

## 1.1 Synopsis

**Protocol Title:** A Phase 3, Randomized, 24-week, Placebo-controlled, Double-blind Study to Assess the Efficacy, Safety and Tolerability of Rocatinlimab (AMG 451) Monotherapy in Adult Subjects With Moderate-to-severe Atopic Dermatitis (AD) (ROCKET-Horizon)

Short Protocol Title: A Phase 3, Placebo-controlled, Double-blind Study Assessing Rocatinlimab (AMG 451) Monotherapy in Moderate-to-severe AD (ROCKET-Horizon)

**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 et al, 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, 2009). Rocatinlimab (formerly known as KHK4083 and AMG 451) 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 **p**hase 2 study (Study 4083-006) evaluating the efficacy, safety, and tolerability of repeated doses of rocatinlimab in subjects with moderate-to-severe AD, and conducted by Amgen partner Kyowa Kirin Co., Ltd, statistically significant improvements in percent change from baseline to week 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 placebo-controlled study will be conducted in adult subjects presenting with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical medications cannot be prescribed medically because of intolerance or safety risks. The study is designed to confirm the efficacy and safety of rocatinlimab monotherapy, and to establish the beneficial impact on the related

patient-reported outcomes including pruritus, skin pain, sleep loss, and impaired quality of life.

**Benefit/Risk Assessment**

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

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

**Objectives and Endpoints/Estimands**

| Objectives | Endpoints |
|---|---|
| **Coprimary** | |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24, assessed using Validated Investigator's Global | • Achieving a vIGA-AD score of 0 (clear) or 1 (almost clear) with ≥ 2-point reduction from baseline (vIGA-AD 0/1) at week 24 |

| | |
|---|---|
| Assessment for Atopic Dermatitis (vIGA-AD™) | |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24, assessed using Eczema Area and Severity Index (EASI) | • Achieving ≥ 75% reduction from baseline in EASI score (EASI 75) at week 24 |
| **Key Secondary** | |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16, assessed using EASI | • Achieving EASI 75 at week 16 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16, assessed using vIGA-AD | • Achieving vIGA-AD 0/1 at week 16 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16 and week 24 on the patient-reported outcome (PRO) measure of pruritus | • Achieving [redacted] from baseline in weekly average of daily worst pruritus numeric rating scale (NRS) score at week 16 in subjects with baseline weekly average of daily worst pruritus NRS score [redacted]<br>• Achieving [redacted] from baseline in weekly average of daily worst pruritus NRS score at week 24 in subjects with baseline weekly average of daily worst pruritus NRS score [redacted] |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24, assessed using EASI | • Achieving ≥ 90% reduction from baseline in EASI score (EASI 90) at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of atopic dermatitis (AD) skin pain | • **Achieving [redacted] from baseline in weekly average of AD skin pain NRS score at week 24 in subjects with baseline weekly average of AD skin pain NRS score** [redacted] |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24, assessed 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 week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with | • Achieving a [redacted] |

| | |
|---|---|
| placebo on [redacted] | |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo on [redacted] | • Achieving a [redacted] |
| **Other Secondary** | |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16 and week 24 on the PRO measure of pruritus | • Change from baseline in weekly average of daily worst pruritus NRS score at week 16<br>• Change from baseline in weekly average of daily worst pruritus NRS score at week 24<br>• Change from baseline in SCORing Atopic Dermatitis (SCORAD) itch visual analogue scale (VAS) score at week 16<br>• Change from baseline in SCORAD itch VAS score at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of **Dermatology Life Quality Index (**DLQI**)** | • Achieving [redacted] from baseline in DLQI score at week 24 in subjects with baseline DLQI score [redacted]<br>• **Change from baseline in DLQI score at week 24** |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of Patient Oriented Eczema Measure (POEM) | • Achieving [redacted] from baseline in POEM score at week 24 in subjects with baseline POEM score [redacted]<br>• Change from baseline in POEM score at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16 **and week 24** on the PRO measure of AD skin pain | • **Achieving [redacted] rom baseline in weekly average of AD skin pain NRS score at week 16 in subjects with baseline weekly average of AD skin pain NRS score** [redacted]<br>• **Change from baseline in weekly average of daily AD skin pain NRS score at week 24**<br>• Change from baseline in weekly average of daily AD skin pain NRS score at week 16<br>• **Achieving [redacted] from baseline in weekly average of AD skin pain NRS score at week 24 in** |

| | |
|---|---|
| | **subjects with baseline weekly average of AD skin pain NRS score** [redacted]<br>• **Achieving** [redacted] **rom baseline in weekly average of AD skin pain NRS score at week 16 in subjects with baseline weekly average of AD skin pain NRS score** [redacted] |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of sleep disturbance | • Change from baseline in weekly average of **daily** sleep disturbance NRS score at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) | • Achieving HADS-anxiety subscale score [redacted]at week 24 in subjects with baseline HADS-anxiety subscale score [redacted]<br>• Achieving HADS-depression subscale score [redacted] at week 24 in subjects with baseline HADS-depression subscale score [redacted]<br>• Change from baseline in HADS-anxiety subscale score at week 24<br>• Change from baseline in HADS-depression subscale score at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the SCORAD | • Achieving [redacted] from baseline in SCORAD score at week 24 in subjects with baseline SCORAD score [redacted] |
| **Safety and Immunogenicity** | |
| • To characterize the safety and tolerability of rocatinlimab in the proposed population | • Treatment-emergent adverse events (including clinically significant changes in laboratory values and vital signs) and serious adverse events |
| [redacted] | |

**Primary Estimands**

Two intercurrent events will be considered to estimate the treatment effects: initiation of rescue therapy for AD (Table 6-3) and permanent discontinuation of investigational product without rescue therapy for AD. Subjects are encouraged to complete all

remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 24 after permanent discontinuation of investigational product for evaluation of endpoints (see Section 1.3).

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

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

**Overall Design**

This is a phase 3, randomized, 24-week, placebo-controlled, double-blind study to evaluate the efficacy, safety, and tolerability of rocatinlimab [redacted] mg monotherapy in adult subjects with moderate-to-severe AD with inadequate response to topical medications. Prior biologic or targeted-small molecules (eg, Janus kinase [JAK] inhibitors) use is allowed with an adequate washout period.

Subjects will undergo an initial screening visit to confirm eligibility requirements, and those who meet all eligibility criteria that can be confirmed at the initial screening visit will be assigned an electronic diary (eDiary) device where they will be expected to complete

the daily questionnaires each day throughout the screening period. The screening period, which starts with the initial screening visit and ends with the day 1 prerandomization visit, will be a minimum of [redacted] days and a maximum of [redacted] days. At the day 1 prerandomization visit, subjects who meet all eligibility criteria will be randomized. Subjects who do not meet all eligibility requirements at the initial screening and day 1 prerandomization visits will be considered screen failures. Subjects may be allowed to rescreen once.

**Treatment Period**

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

- Rocatinlimab [redacted] mg every 4 weeks (Q4W) with a loading dose at week 2 (N = [redacted])
- Placebo Q4W with a loading dose at week 2 (N = [redacted])

Randomization will be stratified by baseline disease severity (moderate Validated Investigator's Global Assessment for Atopic Dermatitis [vIGA-AD score = 3] versus severe [vIGA-AD score = 4]), and geographic region (Japan versus non-Japan Asian countries versus rest of world).

Subjects may be eligible to enroll in a long-term maintenance study (Study [redacted]

**Rescue Therapies for AD**

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

**Discontinuation of Study Treatment and Subject Discontinuation**

Subjects who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 24 for the evaluation of the coprimary endpoints, which will correspond to their End of Treatment (EOT) visit (see Section 1.3).

Subjects who permanently discontinue investigational product and do not complete the remaining study visits through week 24 should complete the EOT visit at the next scheduled visit following the last dose of the investigational product.

**Safety Follow-up**

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

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

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

**Number of Subjects**

Approximately [redacted]

**Summary of Subject Eligibility Criteria**

- Males or females aged ≥ 18 years 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 of informed consent.
- Prior to informed consent, history of inadequate response to [redacted] (refer to Table 11-4) ([redacted]) or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks)
  [redacted]

[redacted]

- Presence of moderate-to-severe AD at both initial screening and day 1 prerandomization visit, defined as EASI score ≥ 16, vIGA-AD score ≥ 3 (on the 0 to 4 vIGA-AD scale, in which 3 is moderate and 4 is severe) and ≥ 10% [redacted]. Additionally, patient-reported worst pruritus NRS ≥ 4 based on a single-question item with 7-day recall is required at initial screening.

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

**Treatments**

The blinded treatment during the 24-week treatment period includes:

- Rocatinlimab [redacted] mg **Q4W with a loading dose at week 2**
- Placebo **Q4W with a loading dose at week 2**

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

**Statistical Considerations**

Approximately [redacted] subjects will be randomized in a [redacted] ratio to 2 treatment groups as follows:

- Rocatinlimab [redacted] mg (n = [redacted]
- Placebo (n = [redacted])

[redacted]

[redacted]

[redacted]

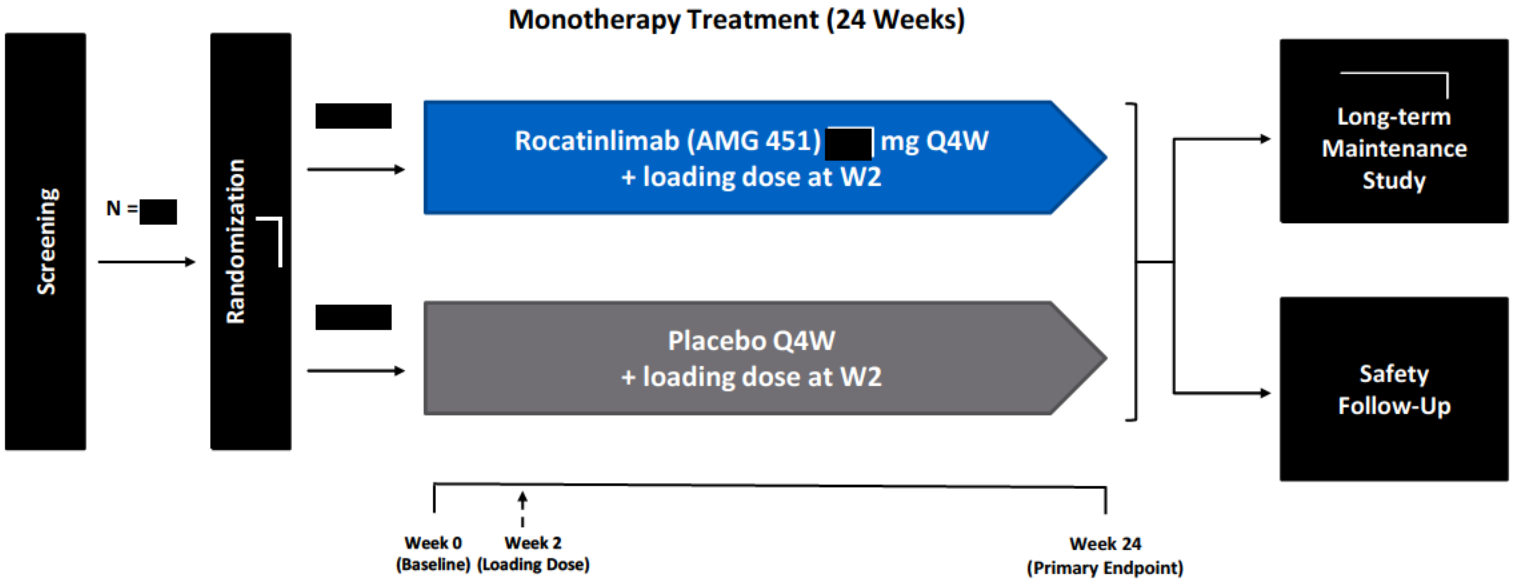
**Statistical Hypotheses**

The primary hypothesis is that rocatinlimab [redacted] mg is superior to placebo as treatment in subjects with moderate-to-severe AD, as assessed by the coprimary endpoints, and both coprimary endpoints need to achieve statistical significance to declare study success.

**Sponsor Name:** Amgen

## 1.2 Study Schema

**Figure 1-1. Study Schema**




N = number of subjects; Q4W = every 4 weeks; W = week.

## 1.3 Schedule of Activities (SoA)

**Table 1-1. Schedule of Activities**

| Procedure | Screening Period[a] (Up to [redacted] days) | | Treatment Period[b] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening | Day 1 Pre rand | Day 1 Post rand[c] | [redacted] | | | | | | | EOS/SFU (± 3d) | Unscheduled Visit[d] |
| **GENERAL AND SAFETY ASSESSMENTS** | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | X[c] | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Physical examination[bb] | X | | | | | | X | | | X | X | X |
| Vital signs[e] | X | | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | |
| Body weight | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Cardiovascular medical history | X | | | | | | | | | | | |
| Dermatologic medical history | X | | | | | | | | | | | |
| Immunologic medical history | X | | | | | | | | | | | |
| Medication history | X | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | |

| Procedure | Screening Period[a] (Up to [redacted] days) | | Treatment Period[b] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening | Day 1 Pre rand | Day 1 Post rand[c] | [redacted] | | | | | | | EOS/SFU (± 3d) | Unscheduled Visit[d] |
| Substance abuse history[g] | X | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | |
| ECG | X | | | | | | X | | | X | | X |
| Cardiovascular risk factors | | | X | | | | | | | | | |
| Adverse events | | | X | X | X | X | X | X | X | X | X | X |
| Serious adverse events[i] | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant therapies review | X | X | | X | X | X | X | X | X | X | X | X |
| Screening TB risk assessment questionnaire | | X | | | | | | | | | | |
| On-study TB risk assessment questionnaire | | | | | | | X | | | X | X | |
| **LABORATORY ASSESSMENTS[j]** | | | | | | | | | | | | |
| Coagulation | X | | | | | | | | | | | X |
| HIV, Hepatitis B and C screening[k] | X | | | | | | | | | | | X |
| Hepatitis B DNA (reactivation monitoring only)[x] | | | | | | | | | | X | | X |
| Serum pregnancy test (females of childbearing potential only)[l] | X | | | | | | | | | | | X |

| Procedure | Screening Period[a] (Up to [redacted] days) | | Treatment Period[b] | | | | | | | | EOS/SFU (± 3d) | Unscheduled Visit[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening | Day 1 Pre rand | Day 1 Post rand[c] | [redacted] | | | | | | | | |
| Urine pregnancy test (females of childbearing potential only)[l] | | X | | | X | X | X | X | X | X | X | X |
| Hematology | X | | X | | X | X | | X | | X | X | X |
| Chemistry | X | | X | | | X | | X | | X | X | X |
| Urinalysis[m] | X | | | | | | | | | | | X |
| QuantiFERON GOLD[n] | X | | | | | | | | | | X | X |
| [redacted] | | | | | | | | | | | | |
| **EFFICACY/CLINICAL OUTCOME ASSESSMENTS – ASSESSED BY INVESTIGATOR[z]** | | | | | | | | | | | | |
| vIGA-AD | X | X | | X | X | X | X | X | X | X | | X |
| AD morphology assessment[o] | | | | X | X | X | X | X | X | X | | X |
| EASI | X | X | | X | X | X | X | X | X | X | | X |

| Procedure | Screening Period[a] (Up to [redacted] days) | | Treatment Period[b] | | | | | | | | EOS/SFU (± 3d) | Unscheduled Visit[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening | Day 1 Pre rand | Day 1 Post rand[c] | [redacted] | | | | | | | | |
| [redacted] | | | | | | | | | | | | |
| SCORAD (investigator facing) | | | X | X | X | X | X | X | X | X | | |
| [redacted] | | | | | | | | | | | | |
| **EFFICACY/CLINICAL OUTCOME ASSESSMENTS - ASSESSED BY SUBJECT[z]** | | | | | | | | | | | | |
| Site assigns e-diary | X | | | | | | | | | | | |
| Worst pruritus NRS[s,t] | ←==========Daily e-Diary==========→ | | | | | | | | | | | |
| AD skin pain NRS[t] | ←==========Daily e-Diary==========→ | | | | | | | | | | | |
| Sleep disturbance NRS[t] | ←==========Daily e-Diary==========→ | | | | | | | | | | | |
| SCORAD (subject facing) | | | X | X | X | X | X | X | X | X | | |
| DLQI | | | X | X | | X | | X | | X | | |
| POEM | | | X | | X | X | | X | | X | | |
| HADS | X | X | | X | X | X | X | X | X | X | X | X |
| [redacted] | | | | | | | | | | | | |

| Procedure | Screening Period[a] (Up to [redacted] days) | | Treatment Period[b] | | | | | | | | EOS/SFU (± 3d) | Unscheduled Visit[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening | Day 1 Pre rand | Day 1 Post rand[c] | [redacted] | | | | | | | | |
| **STUDY TREATMENT** | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | |
| Mental health recommendation review[dd] | | X | | X | X | X | X | X | X | X | | |
| [redacted] | | | | | | | | | | | | |

[redacted] AD = atopic dermatitis; [redacted] COA = clinical outcome assessments; [redacted] ema Area and Severity Index; ECG = electrocardiogram; e-Diary = electronic diary; EOS = end of study; EOT = end of treatment; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; HADS = Hospital Anxiety and Depression Scale; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; JAK = Janus kinase; NRS = numeric rating scale; [redacted] POEM = Patient Oriented Eczema Measure; Rand = randomization; SCORAD = SCORing Atopic Dermatitis; SFU – safety follow-up; TB = tuberculosis; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis; W = week.

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

[b] Subjects who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 24 for the evaluation of the coprimary endpoints, which will correspond to their EOT visit. Subjects who permanently discontinue investigational product and do not complete the remaining study visits through week 24, should complete the EOT visit (see W24/EOT in Table 1-1) at the next scheduled visit following the last dose of the investigational product. A safety follow-up visit is required [redacted] after the last dose of investigational product for all subjects who do not enroll into the long-term maintenance study (Study [redacted]

[c] Only certain eligibility criteria will be re-evaluated at the day 1 prerandomization visit. These criteria are required to be met for enrollment/randomization. All baseline assessments at day 1 post-randomization visit must be completed prior to administration of investigational product. See Section 5.1 for additional information.

[d] Unscheduled visits may occur at any timepoint 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.

[redacted]

[g] Alcohol, recreational drugs, and tobacco use

[redacted]

Once the study has ended, the investigator will report to Amgen 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.

[j] To be collected predose.

[k] Hepatitis B DNA testing will be performed for subjects with positive HBsAg and/or HBV core Ab.

[l] Additional on-study pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.

[m] Additional urinalysis can be performed on-study at the investigator's discretion per standard of care.

[n] Refer to Section 8.10.1 for additional information on tuberculosis assessments.

[o] Only for subjects who achieve vIGA-AD score of 1.

[redacted]

This screening assessment will be collected using the site tablet at the initial screening visit. The assessment will have a 7-day recall. Throughout the rest of the study, the daily recall NRS will be collected on the subject's handheld device.

[t] Daily NRS diary entries to begin the day after the initial screening visit through week 24/EOT visit.

[redacted]

[v] Subjects must be monitored for 2 hours following at least the first 2 doses of investigational product on day 1 and week 2. 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. Refer to Section 8.4.2 for additional information on post-dose monitoring.

[w] Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature must be measured only at the end of the 2-hour post-dose monitoring period before subject is discharged. (X): as needed.

[x] For subjects with positive HBsAg and/or HBV core Ab at initial screening. Any additional testing may be performed per investigator's discretion. For sites and subjects participating in the European Economic Area (EEA), please refer to Section 11.9 (Appendix 9).

[y] For subjects who enroll into the long-term maintenance study (Study [redacted] W24/EOT visit will be considered EOS visit, and a safety follow-up visit will not be required. For subjects who do not enroll into the long-term maintenance study (Study [redacted] a SFU visit will be required for subjects who have not been followed for at least [redacted] after the last dose of investigational product.

[z] Clinical outcome assessments should be performed prior to any other activity at each visit.

[redacted]

[bb] Complete physical examination will be conducted at screening, and symptom-directed physical examination at subsequent study visits at the discretion of the investigator per standard of care. Refer to Section 8.2.4 for additional information.

[redacted]

[dd] 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 et al, 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, 2009). Rocatinlimab (formerly known as KHK4083 and AMG 451) 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 **p**hase 2 study (Study 4083-006) evaluating the efficacy, safety, and tolerability of repeated doses of rocatinlimab in subjects with moderate-to-severe AD, and conducted by Amgen partner Kyowa Kirin Co., Ltd, statistically significant improvements in percent change from baseline to week 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 placebo-controlled study will be conducted in adult subjects presenting with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical medications cannot be prescribed medically because of intolerance or safety risks. The study is designed to confirm the efficacy and safety of rocatinlimab monotherapy, and to establish the beneficial impact on the related patient-reported outcomes including pruritus, skin pain, sleep loss, and impaired quality of life.

## 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 [redacted] 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, [redacted], 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 IL-4Rα 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 for patients 6 months and older with moderate-to-severe AD who are candidates for systemic therapy, and in Japan for adults with moderate-to-severe AD. While dupilumab has shown favorable efficacy data in moderate-to-severe AD, nearly half of the patients receiving 300 mg every 1 or 2 weeks fail to reach achievement of ≥ 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 et al, 2021). Therefore, there is still a large unmet need for novel biologic therapies with different mechanism of action and with improved safety profile for this population.

### 2.2.2 Amgen Investigational Product Background: Rocatinlimab

Rocatinlimab (formerly known as KHK4083 and AMG 451) 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

[redacted]

As of the end of the phase 2b study 4083-006, approximately [redacted] subjects in the entire development program had received at least 1 dose of rocatinlimab, including healthy subjects, and subjects with plaque psoriasis, ulcerative colitis, and AD, from which [redacted] have been treated for at least 6 months and [redacted] subjects have been exposed for 1 year.

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

[redacted]

The mechanism of action of rocatinlimab and its immunomodulatory activity may suggest potential effects on host's response to infections. No imbalance in subject incidence of infections has been observed in the completed studies to date.

As further described in this protocol, only the SC route of administration is planned, which limits the risk of adverse effects associated with IV infusion. Overall, SC administration is associated with lower incidence of systemic reactions and/or lower severity of acute reactions that tend to be local (Mateos et al, 2020, Davies et al, 2017, Assouline et al, 2016). In addition, eligibility criteria have been implemented to exclude subjects vulnerable to acute allergic reactions. All subjects will be observed after investigational product administration, and will be monitored throughout the study with hematology and standard adverse event and serious adverse event reporting.

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

### 2.3.1 COVID-19

Amgen closely monitors the coronavirus **disease**-19 (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.

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

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

Subjects enrolled in this study are permitted to receive vaccinations for COVID-19 as described in Section 6.7.2.

## 3. Objectives and Endpoints/Estimands

| Objectives | Endpoints |
|---|---|
| **Coprimary** | |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24, assessed using Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD™) | • Achieving a vIGA-AD score of 0 (clear) or 1 (almost clear) with [redacted] from baseline (vIGA-AD 0/1) at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24, assessed using Eczema Area and Severity Index (EASI) | • Achieving ≥ 75% reduction from baseline in EASI score (EASI 75) at week 24 |
| **Key Secondary** | |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16, assessed using EASI | • Achieving EASI 75 at week 16 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16, assessed using vIGA-AD | • Achieving vIGA-AD 0/1 at week 16 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16 and week 24 on the patient-reported outcome (PRO) measure of pruritus | • Achieving [redacted] from baseline in weekly average of daily worst pruritus numeric rating scale (NRS) score at week 16 in subjects with baseline weekly average of daily worst pruritus NRS score [redacted]<br>• Achieving [redacted] from baseline in weekly average of daily worst pruritus NRS score at week 24 in subjects with baseline weekly average of daily worst pruritus NRS score [redacted] |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24, assessed using EASI | • Achieving ≥ 90% reduction from baseline in EASI score (EASI 90) at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of atopic dermatitis (AD) skin pain | • **Achieving [redacted] from baseline in weekly average of AD skin pain NRS score at week 24 in subjects with baseline weekly average of AD skin pain NRS score** [redacted] |

| | |
|---|---|
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24, assessed 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 week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo on [redacted] | • Achieving a [redacted] |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo on [redacted] | • Achieving a [redacted] |
| **Other Secondary** | |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16 and week 24 on the PRO measure of pruritus | • Change from baseline in weekly average of daily worst pruritus NRS score at week 16<br>• Change from baseline in weekly average of daily worst pruritus NRS score at week 24<br>• Change from baseline in SCORing Atopic Dermatitis (SCORAD) itch visual analogue scale (VAS) score at week 16<br>• Change from baseline in SCORAD itch VAS score at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of **Dermatology Life Quality Index (**DLQI**)** | • Achieving [redacted] rom baseline in DLQI score at week 24 in subjects with baseline DLQI score [redacted]<br>• **Change from baseline in DLQI score at week 24** |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of Patient Oriented Eczema Measure (POEM) | • Achieving [redacted] from baseline in POEM score at week 24 in subjects with baseline POEM score [redacted]<br>• Change from baseline in POEM score at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 16 **and week 24** on the PRO measure of AD skin pain | • **Achieving [redacted] from baseline in weekly average of AD skin pain NRS score at week 16 in subjects with baseline weekly average of AD skin pain NRS score** [redacted] |

| | |
|---|---|
| | • **Change from baseline in weekly average of daily AD skin pain NRS score at week 24**<br>• Change from baseline in weekly average of daily AD skin pain NRS score at week 16<br>• **Achieving [redacted] from baseline in weekly average of AD skin pain NRS score at week 24 in subjects with baseline weekly average of AD skin pain NRS score [redacted]**<br>• **Achieving [redacted] from baseline in weekly average of AD skin pain NRS score at week 16 in subjects with baseline weekly average of AD skin pain NRS score [redacted]** |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of sleep disturbance | • Change from baseline in weekly average of **daily** sleep disturbance NRS score at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the PRO measure of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) | • Achieving HADS-anxiety subscale score [redacted] at week 24 in subjects with baseline HADS-anxiety subscale score [redacted]<br>• Achieving HADS-depression subscale score [redacted] at week 24 in subjects with baseline HADS-depression subscale score [redacted]<br>• Change from baseline in HADS-anxiety subscale score at week 24.<br>• Change from baseline in HADS-depression subscale score at week 24 |
| • To evaluate the efficacy of rocatinlimab [redacted] mg compared with placebo at week 24 on the SCORAD | • Achieving [redacted] from baseline in SCORAD score at week 24 in subjects with baseline SCORAD score [redacted] |
| **Safety and Immunogenicity** | |
| • To characterize the safety and tolerability of rocatinlimab in the proposed population | • Treatment-emergent adverse events (including clinically significant changes in laboratory values and vital signs) and serious adverse events |

[redacted]

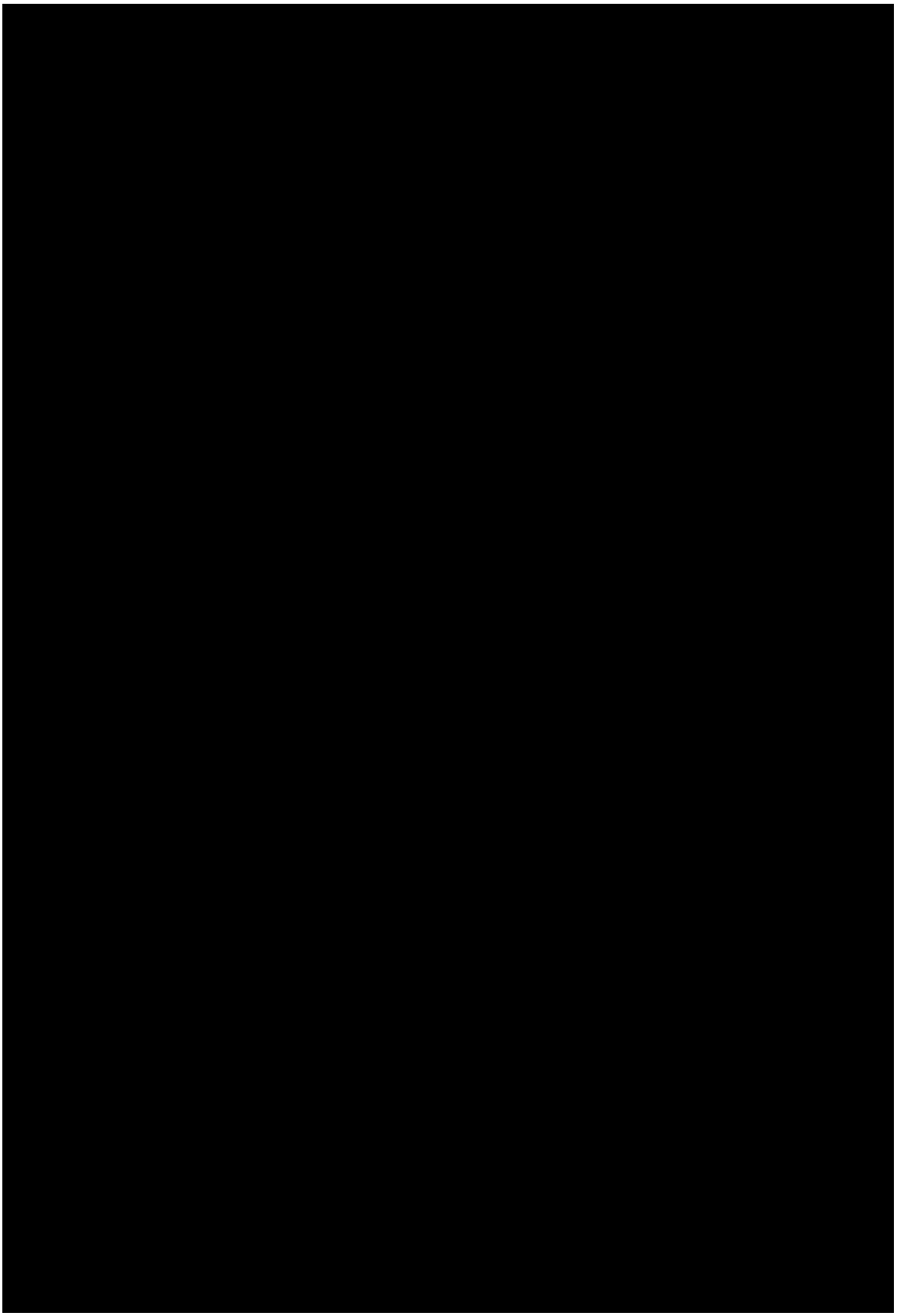
**Primary Estimands**

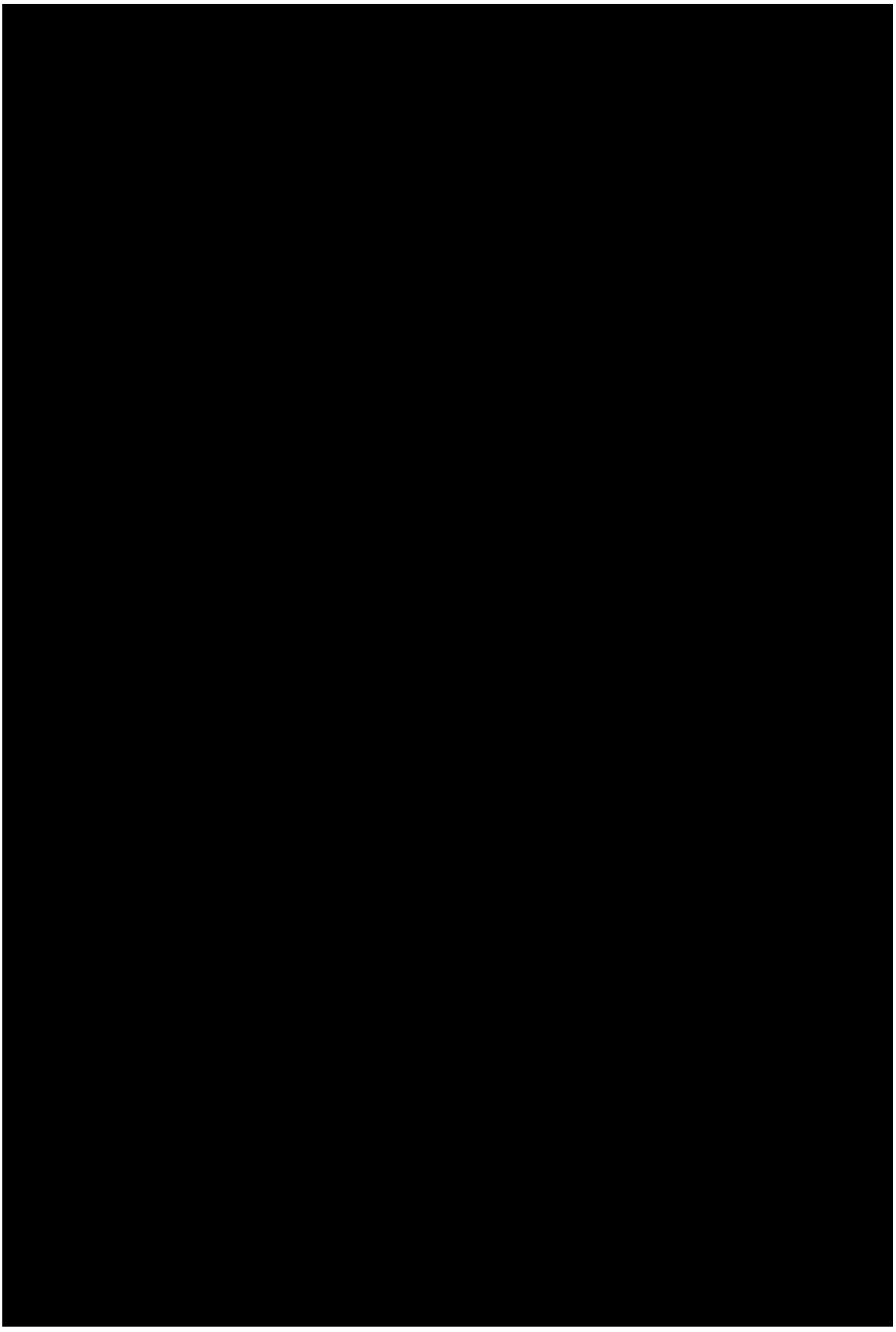
Two intercurrent events will be considered to estimate the treatment effects: initiation of rescue therapy for AD (Table 6-3) and permanent discontinuation of investigational product without rescue therapy for AD. Subjects are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 24 after permanent discontinuation of investigational product for evaluation of endpoints (see Section 1.3).

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

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

| **Objectives** | **Endpoints** |
|---|---|
| **Exploratory** | |
| [redacted] | |





[redacted]

**Exploratory (Pharmacodynamic and Pharmacokinetics)**

[redacted]

## 4. Study Design

### 4.1 Overall Design

This is a phase 3, 24-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of rocatinlimab [redacted] mg monotherapy in adult subjects with moderate-to-severe AD with inadequate response to topical medications. Prior biologic or targeted-small molecules (eg, Janus kinase [JAK] inhibitors) use is allowed with an adequate washout period.

Subjects will undergo an initial screening visit to confirm eligibility requirements, and those who meet all eligibility criteria that can be confirmed at the initial screening visit will be assigned an electronic diary (eDiary) device where they will be expected to complete the daily questionnaires each day throughout the screening period. The screening period, which starts with the initial screening visit and ends with the day 1 prerandomization visit, will be a minimum of [redacted] days and a maximum of [redacted] days. At the day 1 prerandomization visit, subjects who meet all eligibility criteria will be randomized. Subjects who do not meet all eligibility requirements at the initial screening and day 1

prerandomization visits will be considered screen failures. Subjects may be allowed to rescreen once.

**Treatment Period**

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

- Rocatinlimab [redacted] mg Q4W (with a loading dose at week 2) (N = [redacted]
- Placebo Q4W (with a loading dose at week 2) (N = [redacted]

Randomization will be stratified by baseline disease severity (moderate Validated Investigator's Global Assessment for Atopic Dermatitis [vIGA-AD score = 3] versus severe [vIGA-AD score = 4]), and geographic region (Japan versus non-Japan Asian countries versus rest of world).

Subjects may be eligible to enroll in a long-term maintenance study (Study [redacted]

**Rescue Therapies for AD**

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

**Discontinuation of Study Treatment and Subject Discontinuation**

Subjects who permanently discontinue investigational product for any reason during the study are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 24 for the evaluation of the coprimary endpoints, which will correspond to their End of Treatment (EOT) visit (see Section 1.3).

Subjects who permanently discontinue investigational product and do not complete the remaining study visits through week 24 should complete the EOT visit at the next scheduled visit following the last dose of the investigational product.

**Safety Follow-up**

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

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

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

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

### 4.2 Patient Input into the Study Design

Patient input was not obtained for this study.

### 4.3 Justification for Dose

#### 4.3.1 Justification for Investigational Product Dose

This study will be used to investigate rocatinlimab [redacted] mg Q4W for 24 weeks with a loading dose at week 2.

[redacted]

### 4.4 End of Study

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

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

## 5. Study Population

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

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

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (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 subject characteristics.

### 5.1 Inclusion Criteria

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

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

102 Age ≥ 18 years (or ≥ legal adult age within the country if it is older than 18 years) at signing of informed consent.

113 Subject 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.

114 Prior to informed consent, history of inadequate response to [redacted] (refer to Table 11-4) ([redacted]) or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks).

[redacted]

105 EASI score ≥ 16 at initial screening.

106 EASI score ≥ 16 at day 1 prerandomization.

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

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

109 ≥ 10% [redacted] at initial screening.

110 ≥ 10% [redacted] at day 1 prerandomization.

111 Patient-reported Worst Pruritus NRS ≥ 4 based on a single-question item with 7-day recall at initial screening.

112 Subjects must have completed at least 4 days of daily diary entries within the 14 days preceding and including day 1 prerandomization.

## 5.2 Exclusion Criteria

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

### Other Medical Conditions

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

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

203 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 prerandomization 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 subject with detectable hepatitis B Surface Antigen (HbsAg) and/or antibodies to hepatitis B core **(anti-HBc)**. Subjects with detectable HbsAg are required to be virally suppressed with an approved hepatitis B antiviral therapy during the study.

For sites and subjects participating in the European Economic Area (EEA), please refer to Section 11.9 (Appendix 9).

236 Positive or indeterminate QuantiFERON GOLD from central laboratory at initial screening:

- Exception: A positive or indeterminate QuantiFERON test is allowed if ALL of the following are present at day 1 prerandomization per Screening TB Risk Assessment Questionnaire provided by Amgen:
  - No symptoms of tuberculosis (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 prerandomization

For sites and subjects participating in the EEA, please refer to Section 11.9 (Appendix 9).

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.

229 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 prerandomization.

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

212 Severe depression, poorly controlled schizophrenia, or subjects who have had an inpatient psychiatric admission within the last year. Subjects who are receiving a

psychiatric treatment regimen must be stable on treatment for at least 8 weeks prior to study day 1.

213 Any of the following laboratory abnormalities at initial screening:

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

[redacted]

230 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.

231 Recent cardiovascular events including: cerebrovascular accident, myocardial infarction, coronary stenting, or unstable angina within 6 months of day 1 prerandomization.

**Prior/Concomitant Therapy**

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

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

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

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

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

[redacted]

- Topical PDE4 inhibitors

- Other topical immunosuppressive agents
- Combination agents including [redacted], PDE4 inhibitors, or other topical immunosuppressive agents

218 Treatment with live virus including live attenuated vaccination 12 weeks prior to day 1 prerandomization. Inactive vaccination (eg, nonlive or nonreplicating agent) including COVID-19 vaccination, is allowed.

**Prior/Concurrent Clinical Study Experience**

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

238 Currently receiving treatment in another investigational device or drug study, or less than 30 days (16 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.

**Other Exclusions**

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

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

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

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

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

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

## 5.3 Lifestyle Considerations

### 5.3.1 Meals and Dietary Restrictions

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

### 5.3.2 Activity

Emotional stress, defined as general response of the body to external or internal challenges to the AD pathology can impact disease severity. Factors like lifestyle and leisure activities may change the behavior of immune cells in AD with an impact on the evolution of the disease (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 subjects should be encouraged to adhere to usual activity and avoid any activities known to affect their AD.

## 5.4 Subject Enrollment

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

The subject or the subject'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.

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

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

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

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

## 5.5 Screen Failures

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

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

# 6. Study Intervention

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

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

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

## 6.1 Study Interventions Administered

### 6.1.1 Investigational Products

**Table 6-1. Investigational Products**

| Study Treatment Name | Amgen Investigational Product:[a] Rocatinlimab | Placebo |
|---|---|---|
| Dosage Formulation | [redacted] mg/mL<br>Supplied as a single-use, preservative free solution for injection | Placebo will be presented in identical containers, and stored/packaged the same as rocatinlimab |
| Unit Dose Strength(s) | [redacted] mg per vial | N/A |
| Dosage Level(s) | Rocatinlimab [redacted] mg Q4W with a loading dose given at week 2 | Placebo Q4W with a loading dose given at week 2 |
| Route of Administration | SC Injection | |
| Accountability | The quantity of investigational product administered per vial, start date/time, and box number of investigational product are to be recorded on each subject's CRF(s). | |
| [redacted] | | |
| Dosage Preparation | Information regarding dose preparation/administration will be provided to the site. | |

CRF = case report form; N/A = not applicable; IP = investigational product; SC = subcutaneous; Q4W = every 4 weeks.

[a] Rocatinlimab/placebo will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

[redacted]

[redacted]

### 6.1.3 Medical Devices

Medical devices will not be used in this study.

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

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

### 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 (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, subjects may continue investigational product if there is concurrent use of any of these therapies:

- Emollients containing added pharmacological agents with antipruritic, antiseptic, and/or keratolytic properties, such as urea ≥ 20%, ammonium lactate ≥ 12%, or salicylic acid ≥ 3%.
- Antihistamines for treatment of pruritus.

#### 6.1.6.3 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. Guidance for Certain Therapeutics for Non-atopic Dermatitis Related Conditions, Including Prohibited Therapies**

| Therapies if given for non-AD-related conditions | Restrictions | Requires Temporary Interruption or Permanent Discontinuation of Investigational Product |
|---|---|---|
| • Live vaccines<br>• Any investigational product in another device or drug study | Always prohibited | Permanent discontinuation |
| • Systemic corticosteroids (eg, oral, IV, or intramuscular) | Strong recommendation to use alternative non-systemic therapy for non-AD-related indications prior to using systemic therapies | If treatment duration ≤ 2 consecutive weeks<br>• May require temporary Interruption to avoid concurrent administration<br>• No temporary interruption required if systemic corticosteroid and adequate washout period (5 half-lives) have completed by next investigational product dose<br>If treatment duration > 2 consecutive weeks<br>• Permanent discontinuation |
| Conventional immunosuppressive or immunomodulatory agents (non-biologic, non-targeted), eg,<br>• Cyclosporine<br>• Azathioprine<br>• Methotrexate<br>• 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, or TNF inhibitors)<br>• Immunotherapy (eg, PD1 inhibitors), cytotoxic, or cell-depleting therapies (eg, cyclophosphamide)<br>• 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 receptor; TNF = tumor necrosis factor TYK2 = tyrosine kinase 2.

## 6.2 Dose Modification

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

Not applicable.

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

#### 6.2.2.1 Amgen Investigational Product: Rocatinlimab/Placebo

The following adverse events require permanent discontinuation from investigational product:

- Anaphylactic reaction or other serious hypersensitivity/allergic reaction assessed as related to investigational product by the investigator
- Malignancy (excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin).

  For sites and subjects participating in the EEA, please refer to Section 11.9 (Appendix 9).
- Opportunistic infection, such as active TB and other infections whose nature or course may suggest an immunocompromised status.

  For sites and subjects participating in the EEA, please refer to Section 11.9 (Appendix 9).
- Serious or severe infection requiring systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents for longer than 2 weeks
- [redacted]
- Severe depression as assessed by the investigator. The investigator should immediately refer the subject for mental health assessment and treatment, as per local standard of care (see Sections [redacted] 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 investigational product (see Table 6-2 and Table 6-3).

### 6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

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

## 6.3 Preparation/Handling/Storage/Accountability

Guidance and information on drug accountability for the investigational product will be provided to the site. If permitted by local regulations, the site may ship investigational product to the subject. If the site does not have its own courier, shipment can be organized by a third-party courier engaged by sponsor. The courier's information must be included on the Delegation of Authority Form. The investigator is responsible for directing and supervising the shipment and activities of the courier. Subjects should be informed of their responsibilities for receipt, handling, storage, and accountability if site to patient shipments will be performed. Additional guidance will be provided to the site. There is no additional risk to subjects with the Site to Patient process. Site to Patient specific training will be provided and support materials for the sites and subjects as necessary. Management of temperature data and status check of investigational product will be completed post-delivery by way of courier review of the temperature logger.

## 6.4 Measures to Minimize Bias: Randomization and Blinding

### 6.4.1 Method of Treatment Assignment

The randomization for the treatment period as described in Section 4.1 will be performed by IRT according to the randomization list generated by Amgen Global Randomization and Blinding group, and the randomization date will be captured in IRT.

### 6.4.2 Blinding

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

The following assessments will also be considered unblinding information:

[redacted]

Unblinding information will be blinded to all subjects, site personnel, and Amgen as described below (Section 6.4.2.1 and Section 6.4.2.2).

#### 6.4.2.1 Site Personnel Access to Unblinding Information

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

Except for emergency unblinding of individual subjects, unblinding information will not be accessible by investigative sites or subjects prior to all subjects receiving blinded maintenance treatment in the long-term maintenance study (Study [redacted] having switched to open-label treatment or completed the SFU.

#### 6.4.2.2 Access to Unblinding Information by Amgen or Designees

Pre-identified members of the clinical study team will be unblinded in order to conduct the primary analysis (Section 9.4.1.1). Other members of the clinical study team will not have access to unblinding information prior to all subjects receiving blinded maintenance treatment in the long-term maintenance study (Study [redacted] having switched to open-label treatment or completed the SFU.

### 6.5 Treatment Compliance

When subjects are dosed at the site, they may receive rocatinlimab or placebo directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded 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 (Section 6.1), is anticipated to be low. The investigational product will be administered under medical supervision by qualified personnel and the maximum possible dose to be administered in case of dosing preparation error is [redacted] mg. Treatment of overdose of rocatinlimab consists of general supportive measures directed

to the observed clinical effects. There is no known specific antidote for overdose of rocatinlimab. In 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

[redacted]

### 6.7.2 Concomitant Treatment

Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care in accordance with the restrictions listed in Section **6.1.6**. Subjects will be instructed to consult the investigator or other

appropriate study personnel at the site before taking any new medications or supplements during the study.

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

- For those subjects on stable dosing of prescription sleep medications at entry, downward dose adjustments or discontinuation of treatment may occur during the study.
- Non-sedating antihistamines including, but not limited to, acrivastine, bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, mizolastine, and rupatadine are allowed for treatment of allergic conditions other than AD. Use of antihistamines for treatment of pruritus is discouraged during the study.
- Single intra-articular or soft tissue (bursa, tendons, and ligaments) corticosteroid injection is allowed.
- Intranasal or inhaled steroid use is allowed.
- Topical anesthetics and topical and systemic anti-infective medications are allowed.
- Non-live vaccinations (eg, COVID-19) are allowed.
- Ophthalmic drugs containing antihistamines, corticosteroids or other immunosuppressants are allowed.
- Treatment with concomitant therapies for other medical conditions such as diabetes, hypertension, hyperlipidemia, and psychiatric illnesses is permitted during the study.

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

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

### 6.7.3 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 for AD are defined as therapies concordant with AD treatment and are listed in Table 6-3. It is recommended to use topical rescue therapies before considering using systemic rescue.

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

**Table 6-3. Rescue Therapy for Atopic Dermatitis**

| Rescue Therapy for AD | If deemed necessary, when permitted for use | Requires Temporary Interruption or Permanent Discontinuation of Investigational Product |
|---|---|---|
| Topical rescue therapy and phototherapy:<br>[redacted]<br>• Topical PDE4 inhibitors<br>• Other topical immunosuppressive agents with the exception of topical JAK inhibitors (see below)<br>• Combination agents including [redacted] PDE4 inhibitors, or other topical immunosuppressive agents<br>• 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.<br><br>NOTE: Recommend consideration of topical rescue therapies first | If rescue treatment duration ≤ 2 consecutive weeks<br>• May require temporary Interruption to avoid concurrent administration<br>• No temporary interruption required if rescue treatment and an adequate washout period (5 half-lives) have completed by next investigational product dose<br><br>If rescue treatment duration > 2 consecutive weeks<br>• Permanent discontinuation |
| Conventional immunosuppressive systemic therapies (non-biologic, non-targeted), eg,<br>• Cyclosporine<br>• Azathioprine<br>• Methotrexate<br>• Mycophenolate | Use is discouraged during study, however permitted if deemed necessary.<br><br>NOTE: Recommend use of topical rescue therapies before escalating to systemic rescue therapy | Permanent discontinuation |

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

AD = atopic dermatitis; IV = intravenous; JAK = Janus kinase; PDE4 inhibitor = phosphodiesterase 4 inhibitor; [redacted]

## 7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects 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 subject(s) from investigational product, [redacted] device, and/or other , protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1.

### 7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative [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 subject the appropriate processes for discontinuation from investigational product **and/**or [redacted] and must discuss with the subject the possibilities for continuation of the Schedule of Activities (Section 1.3) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and product complaints (including device-related adverse events, as applicable) and must document this decision in the subject's medical records.

Subjects are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures through week 24 for the evaluation of the coprimary endpoints, which will correspond to their EOT visit (see Section 1.3). Subjects 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 subjects 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)
- pregnancy

## 7.2 Subject Discontinuation/Withdrawal From the Study

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

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

### 7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

## 7.3 Lost to Follow-up

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

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

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

# 8. Study Assessments and Procedures

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

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

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

## 8.1 General Study Periods

### 8.1.1 Screening, Enrollment, and/or Randomization

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

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

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

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 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(s) and/or** [redacted] is to be administered last during each visit that it is required.

Subjects may be eligible to enroll in a long-term maintenance study (Study [redacted]

### 8.1.3 End of Treatment

Subjects who permanently discontinue investigational product for any reason before week 24 are encouraged to complete all remaining study visits and procedures with the exception of investigational product administration and post-dose monitoring procedures

through week 24 for the evaluation of the coprimary endpoints, which will correspond to their EOT visit (see Section 1.3).

Subjects who discontinue investigational product and do not complete the remaining study visits through week 24 should complete the EOT visit at the next scheduled visit following the last dose of investigational product (see W24/EOT in Section 1.3).

#### 8.1.4 Safety Follow-up

A SFU visit is required [redacted] after the last dose of investigational product for all subjects who do not continue into the long-term maintenance study (Study [redacted]
An additional SFU visit will not be required for subjects who discontinue investigational product but who complete the remaining study visits for at least [redacted] after the last dose of investigational product before or at week 24.

#### 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 subjects who discontinue study before the defined end of study visit.

### 8.2 General Assessments

#### 8.2.1 Informed Consent

All subjects or their legally authorized representative (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 (see Section 11.3 [Appendix 3] for further details).

If remote consent is used:

1. The subject should be sent a blank informed consent form/informed consent addendum via mail or email.
2. A member of the study site team (investigator or designee) will call the subject to walk through the document via phone and answer questions. The time and date of the phone conversation should be recorded in the subject's medical record.
3. The subject should sign the informed consent form/informed consent addendum after all questions are answered and return the original or scanned copy via mail or email, respectively. The date and time of the subject's consent should be recorded in the medical record. The subject should take a photograph of the

signature page and send it to the person conducting the informed consent discussion.

4. The person who conducted the informed consent discussion should then sign and date the informed consent form/informed consent addendum, when received.

5. A fully signed version of the informed consent form/informed consent addendum should be provided to the subject.

### 8.2.2 Demographics

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

### 8.2.3 Medical History

The **i**nvestigator or designee will collect a complete medical, dermatological, immunological, and surgical history. Medical history will include information on the subject's concurrent medical conditions. The current severity will be collected for each condition that has not resolved. Record all findings on the medical history CRF. The investigator or designee will also collect any cardiovascular history and cardiovascular risk factors.

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

### 8.2.4 Physical Examination

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

[redacted]

### 8.2.8 Mental Health Assessment

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

[redacted]

**Screening**

Investigators must review relevant data at screening, including, but not limited to, medical history, prior and current medications, substance use, [redacted] The investigator should immediately refer the subject to local mental health assessment and treatment as per local standard of care. Subjects ineligible due to depression [redacted] or behavior may be rescreened once after 1 year or 6 months respectively.

**On-Study**

[redacted]

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

[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.

[redacted]

## 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 subject throughout the study whenever possible; a back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation. At each visit, clinical outcome assessments (COAs) are to be performed prior to any other activity specified in the Schedule of Activities (see Section 1.3).

### 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 (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 (Section 1.3). Whenever possible, the vIGA-AD should be assessed by the same investigator at each visit to reduce the inter-rate variability.

#### 8.3.1.2 Atopic Dermatitis Morphology Assessment

To further characterize the clinical features of subjects with vIGA-AD response, additional assessment of AD morphology will be completed for those subjects with a vIGA-AD score of '1 – Almost clear". This will further evaluate the contribution of erythema, induration, papulation, and lichenification at the time of assessment.

#### 8.3.1.3 Eczema Area and Severity Index

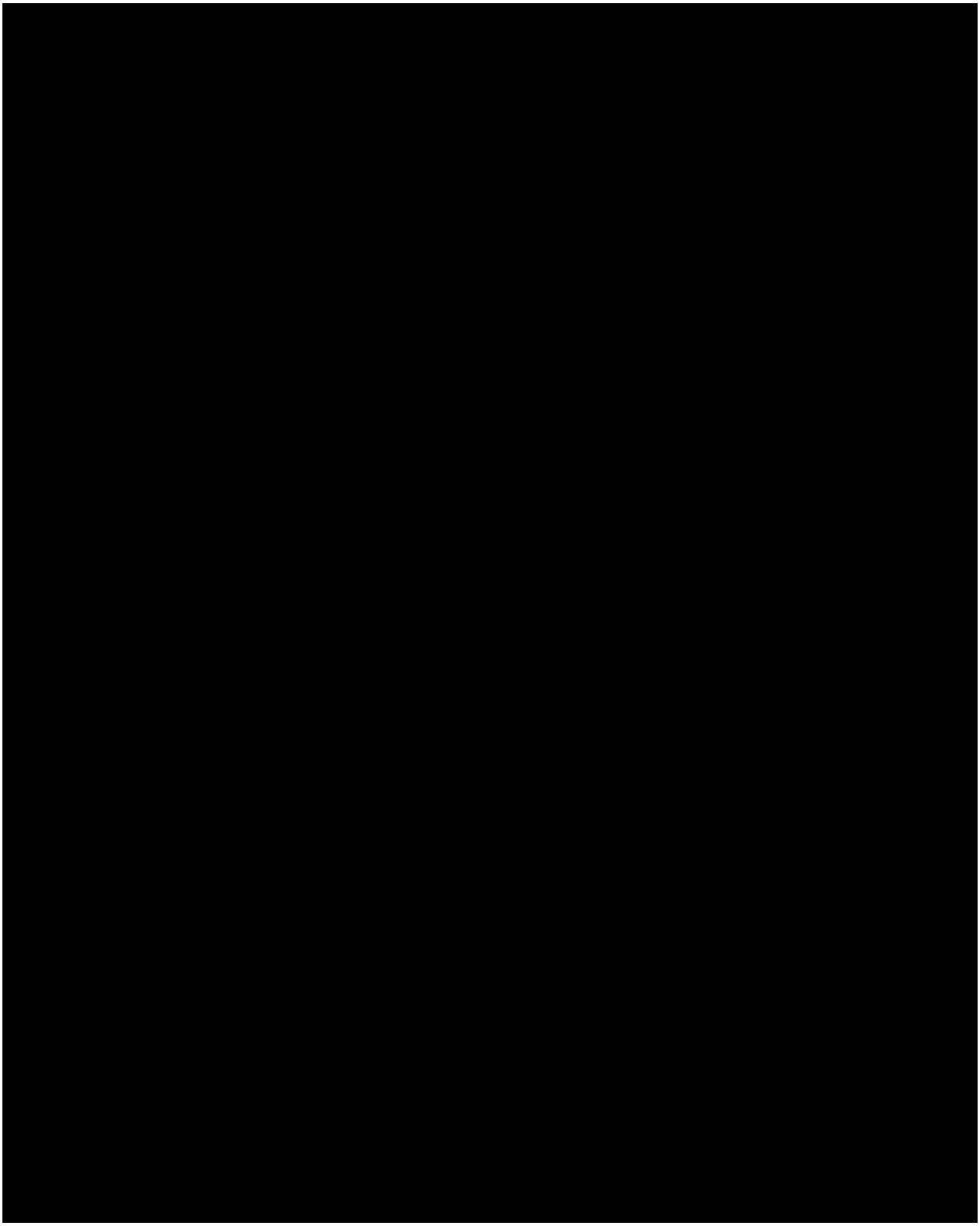
The EASI was designed by modifying the Psoriasis Area and Severity index, which has been widely used in clinical trials and has been established as a well-accepted and standardized instrument for assessing therapeutic response in patients with psoriasis (Schmitt et al, 2007). The EASI evaluates 4 natural 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.

#### 8.3.1.4 Severity Scoring of Atopic Dermatitis

The severity scoring of atopic dermatitis (SCORAD) is a measurement tool for assessing the severity (ie, extent, intensity) of AD using both physician and patient-reported data. The tool evaluates the extent and intensity of the AD lesions, along with subjective symptoms (Kunz et al, 1997). The SCORAD will be assessed at the time points shown in the Schedule of Activities (Section 1.3). The SCORAD should be assessed by the same investigator at each visit, whenever possible, to reduce inter-rater variability. The patient-reported items of the SCORAD will be assessed at the study center at the time points indicated in the Schedule of Activities (Section 1.3).

[redacted]



### 8.3.2 Assessments Completed by Subject

#### 8.3.2.1 Worst Pruritus NRS

In the electronic daily diary assessment, subjects report the severity of pruritus over the past 24 hours. The Worst Pruritus is an NRS comprised of 1 item and represents the numbers 0 to 10. Subjects are asked to rate the intensity of their worst itch using this

scale with 10 being the highest amount of itch. It features high reliability and concurrent validity and is an appropriate choice for all subjects due to its simple format. At initial screening, subjects are asked to rate the intensity of their worst pruritus using this NRS with a 7-day recall.

#### 8.3.2.2 Atopic Dermatitis Skin Pain NRS

In the electronic daily diary assessment, subjects report the severity of AD skin pain over the past 24 hours. The AD Skin Pain is an NRS comprised of 1 item and represents the numbers 0 to 10. Subjects are asked to rate the intensity of their AD skin pain using this scale with 10 being the highest amount of AD skin pain.

#### 8.3.2.3 Sleep Disturbance NRS

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

#### 8.3.2.4 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a 10-item, self-administered questionnaire, and is designed to measure the health-related quality of life of adult patients suffering from skin disease. The DLQI measures patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week.

The DLQI is the most frequently used patient-reported outcome measure in randomized controlled trials in dermatology. The DLQI will be assessed at the study center at the time points indicated in the Schedule of Activities (Section 1.3).

#### 8.3.2.5 Patient Oriented Eczema Measure

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

#### 8.3.2.6 Hospital Anxiety and Depression Scale (HADS)

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

**Table 8-1. Hospital Anxiety and Depression Score Categorization**

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

## 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. Subject must be in a rested and calm state for at least 5 minutes before blood pressure assessment is conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

### 8.4.2 Post-dose Monitoring and Vital Signs

Subjects must be monitored for 2 hours following at least the first 2 doses of the investigational product on day 1 and week 2. Any subject experiencing an acute reaction must receive immediate medical assessment and indicated supportive management according to the institutional standard of care and investigator judgement

until the signs/symptoms of the reaction have resolved. 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 only at the end of the 2-hour post-dose monitoring period before the subject is discharged at specific time points described in the Schedule of Activities (Section 1.3) and Section 8.4.1. Record all measurements on the vital signs CRF.

Clinically significant changes in vital signs as assessed by the investigator and any adverse events are to be reported as per Section 8.4.5.

### 8.4.3 Electrocardiograms (ECGs)

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

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

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

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

### 8.4.5 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 subject that occur after first dose of investigational product through the week 24/EOT visit for subjects who enroll in the long-term maintenance study (Study [redacted] and through the SFU visit for subjects who do not enroll in the long-term maintenance study, are reported using the Events CRF.

Adverse events of special interest (AESIs) including but not exclusive to infections, injection-related reactions, hypersensitivity reactions, major adverse cardiovascular events (MACE), malignancy, neuropsychiatric adverse events, aphthous ulcer, conjunctivitis, and gastrointestinal ulceration/perforation will be monitored.

##### 8.4.5.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the week 24/EOT for subjects who enroll in the long-term extension maintenance study (Study [redacted] and through the SFU visit for subjects who do not enroll in the long-term maintenance study, are reported using the Events CRF.

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

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

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

### 8.4.5.2 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 subject is the preferred method to about adverse event occurrence. If a subject reports or the investigator observes an adverse event of reaction at the site of study drug administration, the investigator is to capture as part of the primary event verbatim in the

Events CRF the location of the reaction together with the type of reaction that better describes the event(s) (eg, injection site pain, injection site erythema, injection site induration, injection site swelling, injection site itching) with clear start and stop dates, rather than only using a general term of "injection site reaction." If there are multiple signs or symptoms at an injection site, each symptom of the event should be reported individually.

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

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

#### 8.4.5.4 Regulatory Reporting Requirements for Safety Information

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

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

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

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

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

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

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

#### 8.4.5.5 Safety Monitoring Plan

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

#### 8.4.5.6 Pregnancy and Lactation

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

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

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

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

**Pregnancy Testing**

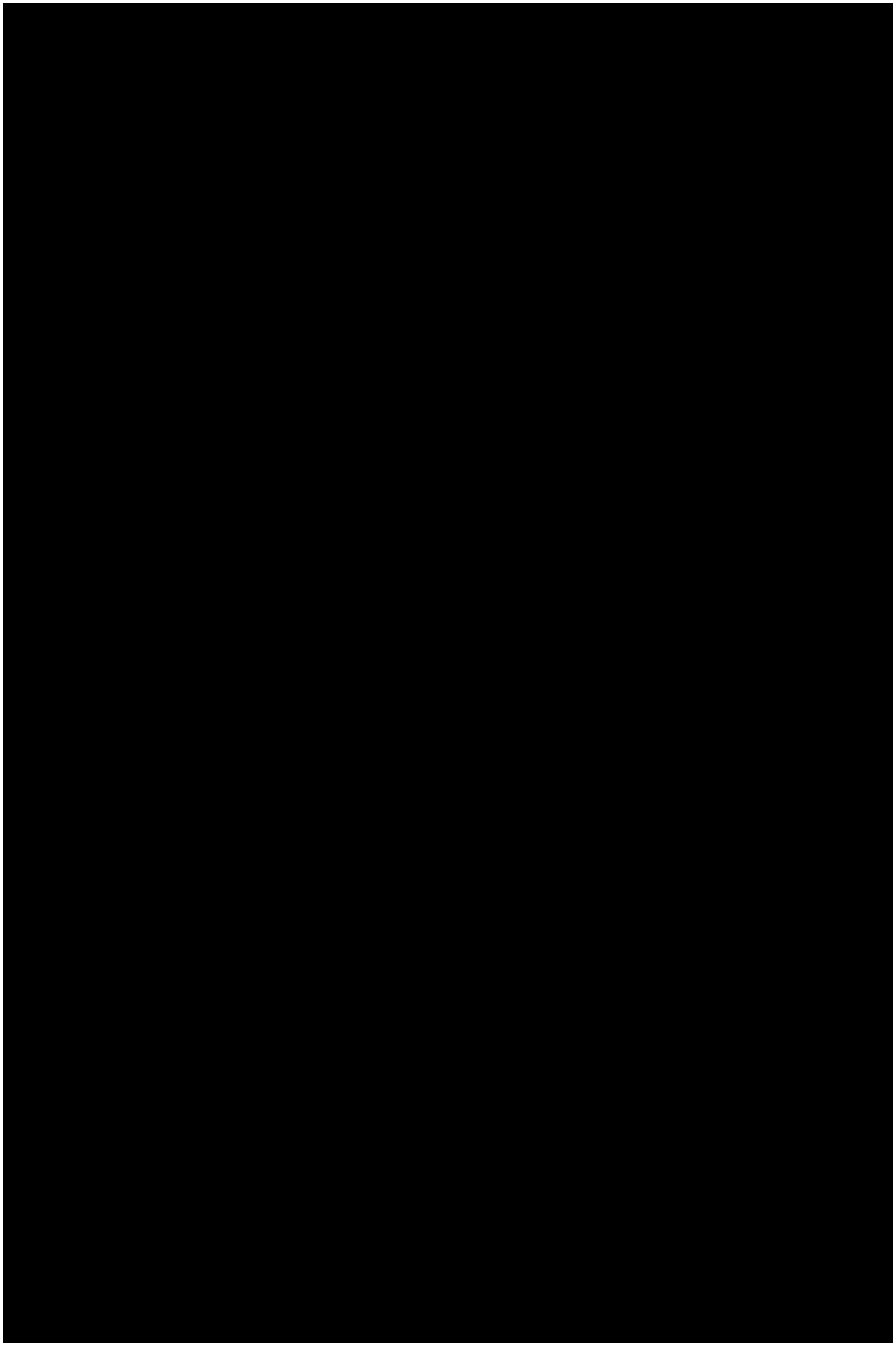
A highly sensitive serum pregnancy test should be completed at initial screening, and a confirmatory urine pregnancy test should be completed on day 1 prerandomization for

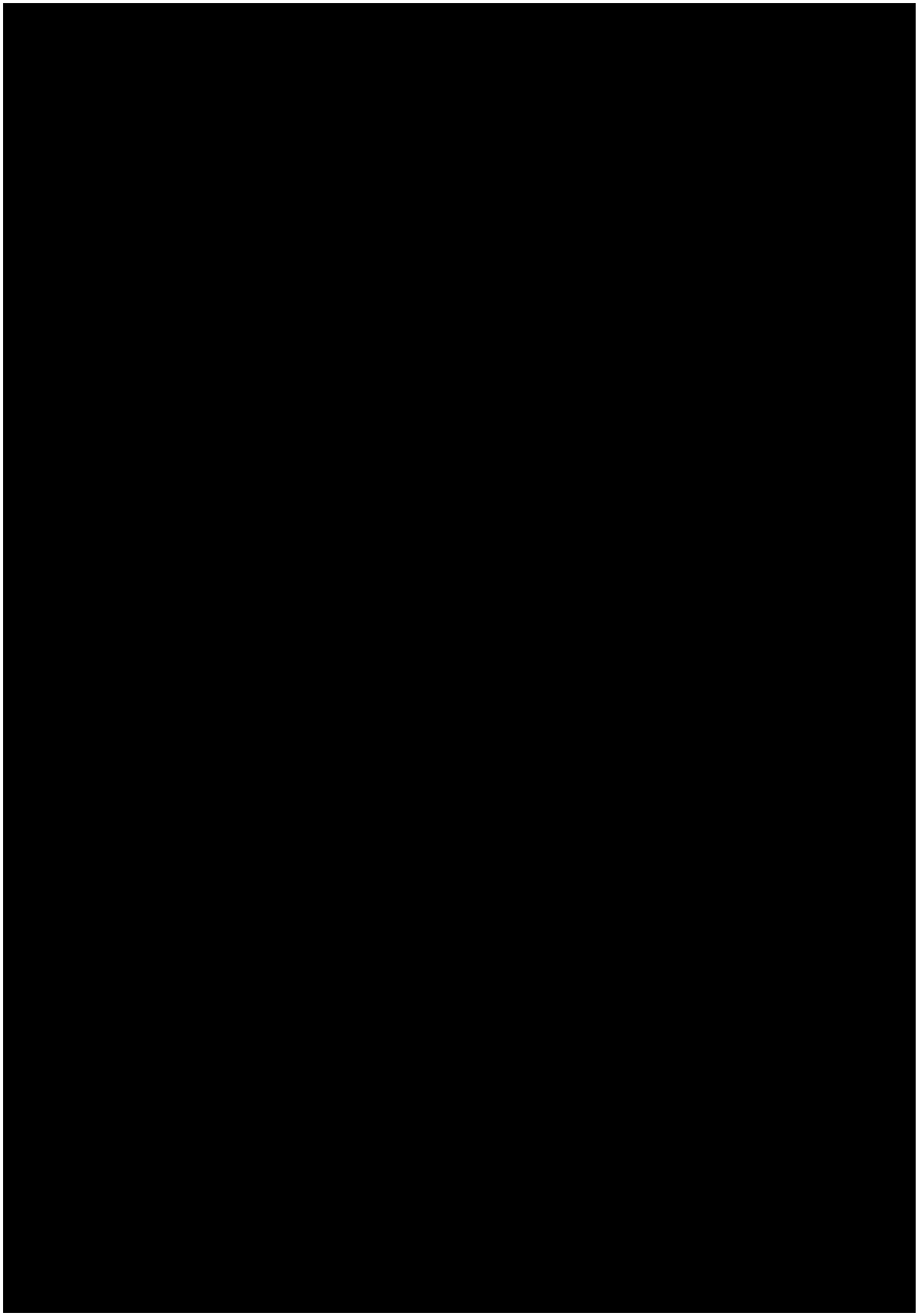
females of childbearing potential, as described in the Schedule of Activities (Section 1.3).

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing should be performed Q4W during treatment with **investigational product** and at the SFU visit when applicable, or 16 weeks after the last dose of investigational product for subjects who discontinue treatment prematurely.

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





[redacted]

## 8.10 Other Assessments

### 8.10.1 Tuberculosis Testing and Tuberculosis Risk Assessment Questionnaire

**Screening**

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

For sites and subjects participating in the EEA, please refer to Section 11.9 (Appendix 9).

**On-Study**

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

- The investigator is to follow local guidelines for the diagnosis and treatment (including prophylaxis) of active or latent TB, as applicable.
- On-study TB testing and chest X-ray may be performed and repeated at the discretion of the investigator.
- Any diagnosis of TB should be reported as a Serious Adverse Event in the Events CRF whether as active or latent TB, as applicable, based on final diagnosis.
- Subjects with confirmed active TB require permanent discontinuation of the investigational product as indicated in Section 6.2.2.1.

- 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 subject should be re-evaluated for signs and symptoms of TB and for prophylactic toxicity within 4 weeks of initiation of prophylactic treatment.
  For sites and subjects participating in the EEA, please refer to Section 11.9 (Appendix 9).

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 subject to be negative based on the absence of symptoms and clinical judgment; if the repeat testing result is positive or indeterminate, then the subject is considered to be positive and additional assessments (eg, 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

The primary hypothesis is that rocatinlimab [redacted] mg is superior to placebo as treatment in subjects with moderate-to-severe AD as assessed by the coprimary endpoints, and both coprimary endpoints need to achieve statistical significance to declare study success.

### 9.2 Sample Size Determination

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

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

[redacted]

## 9.3 Populations for Analysis

The following populations are defined:

| Population | Description |
|---|---|
| Full Analysis Set | All randomized subjects. Subjects will be analyzed according to the randomized treatment. |
| Safety Analysis Set | All subjects who receive at least 1 dose of investigational product. Subjects will be analyzed according to the actual treatment they received. |

### 9.3.1 Covariates

All analyses of efficacy endpoints will be adjusted for the effect of the stratification factors, including baseline disease severity (vIGA-AD score of 3 [moderate] versus 4 [severe] and geographic region (Japan versus non-Japan Asian countries versus rest of world), as well as baseline value of the efficacy endpoint of interest, when applicable.

### 9.3.2 Subgroups

The coprimary and selected **key** secondary endpoints will be analyzed by but not limited to the following subgroups:

- age group (18 to < 40 years**,** 40 to < 65 years**,** ≥ 65 years)
- sex (male, female)
- geographic region (Japan versus non-Japan Asian countries versus rest of world)
- baseline weight group (< **75 kg**, ≥ **75 kg**)
- baseline body mass index (< **25 kg/m$^2$**, ≥ **25 kg/m$^2$**)
- baseline disease severity (moderate [vIGA-AD = 3], severe [vIGA-AD = 4])
- prior use of systemic therapy for the treatment of AD (yes, no)
- prior failure to systemic therapy for AD due to inadequate response or adverse reaction (yes, no)

## 9.4 Statistical Analyses

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

### 9.4.1 Planned Analyses

#### 9.4.1.1 Primary Analysis

The primary analysis will be conducted when all subjects have completed the week 24/EOT visit, and the data have been entered, cleaned, and locked. The objective of the primary analysis is to assess complete efficacy and safety data through week 24 and additional safety data available during SFU as of the data cutoff date.

#### 9.4.1.2 Final Analysis

The final analysis will be conducted at the end of the study when all subjects have completed the EOS visit, and the data have been entered, cleaned, and locked.

The objective of the final analysis is to assess complete safety data through EOS on all subjects over the entire study period.

### 9.4.2 Methods of Analyses

#### 9.4.2.1 General Considerations

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

[redacted]

#### 9.4.2.2 Efficacy Analyses

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Binary** | The primary estimand for a binary endpoint is to measure the effect of rocatinlimab as assessed by the difference in response rates between rocatinlimab [redacted] mg and placebo among randomized subjects within moderate-to-severe AD populations without rescue therapy for AD, regardless of permanent discontinuation of investigational product. Subjects initiating rescue therapy for AD will be classified as nonresponders at all subsequent time points (composite strategy reflecting lack of response). For subjects who do not use rescue therapy for AD but permanently discontinue investigational product, data retrieved after permanent discontinuation of investigational product will be included as collected (treatment policy strategy).<br>The primary **method for handling remaining missing responses will be** [redacted] **Additional s**ensitivity analyses using [redacted] based on **the** assumption of [redacted] |

| Endpoint | Statistical Analysis Methods |
|---|---|
| | [redacted] will be conducted. **Details about missing data imputation will be** specified in the SAP.<br>**The** analysis of the [redacted] between rocatinlimab [redacted] mg and placebo, stratified by randomization strata. The corresponding 95% CI based on [redacted] will be provided. The p-value will be based on the common odds ratio using the [redacted] |
| **Continuous** | The primary estimand for a continuous endpoint is to measure the effect of rocatinlimab as assessed by the difference in **means of** change **or percent change** from baseline value between rocatinlimab [redacted] mg and placebo in randomized subjects within moderate-to-severe AD population without **therapy** medication for AD, regardless of permanent discontinuation of investigational product. Subjects initiating rescue therapy for AD will be included in the analysis, and each subject's worst observation, including baseline value, before initiation of rescue therapy for AD will be carried forward (WOCF) to all subsequent time points (composite strategy reflecting lack of response). For subjects who do not use rescue therapy for AD but permanently discontinue **investigational product**, data retrieved after permanent discontinuation of investigational product will be included as collected (treatment policy strategy).<br>**The remaining missing continuous data will be imputed using** [redacted] **Treatment comparisons** of the continuous endpoint will be performed [redacted], and relevant baseline value as covariates. Treatment difference **in least square means between rocatinlimab** [redacted] **mg and placebo**, 95% CI and p-value will be **provided.** |

#### 9.4.2.3 Safety Analyses

##### 9.4.2.3.1 Adverse Events

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

##### 9.4.2.3.2 Laboratory Test Results

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

#### 9.4.2.3.3 Vital Signs

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

#### 9.4.2.3.4 Electrocardiogram

The ECG measurements in this clinical study are to be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials. The subject incidence of abnormal ECG diagnosis will be summarized by treatment group.

#### 9.4.2.3.5 Antibody Formation

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

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

#### 9.4.2.3.6 Exposure to Investigational Product

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

#### 9.4.2.3.7 Exposure to Concomitant Medication

Number and percentage of subjects receiving rescue therapies will be summarized by category for each treatment group.

### 9.4.2.4 Other Analyses

Not applicable.

## 10. References

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# 11. Appendices

## 11.1 Appendix 1. List of Abbreviations

| Abbreviation | Explanation |
|---|---|
| AD | atopic dermatitis |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransaminase |
| ANCOVA | analysis of covariance |
| **Anti-HBc** | **antibodies to hepatitis B core** |
| AST | aspartate aminotransaminase |
| AUC | area under the concentration-time curve |
| BIL | bilirubin |
| [redacted] | |
| CFR | U.S. Code of Federal Regulations |
| $C_{max}$ | maximum plasma concentration |
| [redacted] | |
| COVID-19 | coronavirus disease-19 |
| CRF | **c**ase **r**eport **f**orm |
| CRO | contract research organization |
| [redacted] | |
| DILI | drug induced liver injury |
| DLQI | Dermatology Life Quality Index |
| DMC | data monitoring committee |
| EASI | Eczema Area and Severity Index |
| [redacted] | |
| EASI 75 | achievement of ≥75% reduction from baseline in EASI score |
| EASI 90 | achievement of ≥ 90% reduction from baseline in EASI score |
| [redacted] | |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| eDiary | electronic diary |
| EEA | European Economic Area |
| EMR | **E**lectronic **M**edical **R**ecord |
| EOS | end of study |
| EOT | end of treatment |
| [redacted] | |
| FSH | Follicle-stimulating hormone |

| | |
|---|---|
| GCP | Good Clinical Practice |
| HADS | Hospital Anxiety and Depression Scale |
| HBsAg | hepatitis B Surface Antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| IB | **I**nvestigator's brochure |
| IBG | Independent Biostatistics Group |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IGA | Investigator's Global Assessment |
| IgG | immunoglobulin G |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| IV | intravenous |
| JAK | janus kinase |
| NCT | National Clinical Trials |
| NRS | numeric rating scale |
| OX40 | CD134 |
| OX40L | OX40 Ligand |
| PCR | polymerase chain reaction |
| PDE4 | phosphodiesterase 4 |
| PI | principal investigator |
| POEM | Patient Oriented Eczema Measure |
| PUBD | potentially unblinding data |
| 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 |
| SCORAD | scoring atopic dermatitis |
| SFU | safety follow-up |
| TARC | thymus and activation-regulated chemokine |
| TB | tuberculosis |
| TBL | total bilirubin |
| [redacted] | |
| Th2 | t helper type 2 cell |
| ULN | upper limit of normal |
| US | United States |
| VAS | visual analogue scale |
| vIGA-AD | Validated Investigator's Global Assessment for Atopic Dermatitis |
| vIGA-AD 0/1 | Achieving a vIGA-AD score of 0 (clear) or 1 (almost clear) with≥ 2-point reduction from baseline |
| vIGA-AD 0 | Achieving a vIGA-AD score of 0 (clear) with ≥ 2-point reduction from baseline |
| vIGA-AD 1 | Achieving a vIGA-AD score of 1 (almost clear) with ≥ 2-point reduction from baseline |
| WOCF | Worst Observation Carried Forward |

## 11.2 Appendix 2. Clinical Laboratory Tests

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

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

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

**Table 11-1. Analyte Listing**

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

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

[redacted]

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

**Table 11-2. 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,<br>Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody |
| Toxicology | Acetaminophen |

AB = antibody; 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; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

## 11.3 Appendix 3. Study Governance Considerations

### Data Monitoring Committee(s)

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

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

### Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, informed consent form, investigator's brochure (IB), and other relevant documents (eg, subject 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 subjects into the study and shipment of Amgen investigational product.

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

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

The investigator will be responsible for the following:

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

**Informed Consent Process**

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

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative (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.

Subjects must be informed that their participation is voluntary. Subjects 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 subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

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

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

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

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

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

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

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

The informed consent form will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining

specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

**Data Protection/Subject Confidentiality**

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

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

On the **c**ase **r**eport **f**orm (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

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

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

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

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

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the Sponsor's systems. The **s**ponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The **s**ponsor

has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the Sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

**Publication Policy**

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

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

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public

responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

**Investigator Signatory Obligations**

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

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

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

**Monitoring Arrangements**

**Data Quality Assurance**

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

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

The sponsor or designee 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 subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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

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

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global 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.

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

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

**Source Documents**

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

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record

of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

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

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

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, 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] and/or medical device(s) or combination product(s) documentation, as applicable

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

**Remote Source Data Review and Verification**

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those subjects who participate in the study 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 2-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 **i**nvestigator reserve the right to terminate the **i**nvestigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

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

**Compensation**

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

**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 subject irrespective of a causal relationship with the study treatment.<br>• 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.<br>• 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, electrocardiograms, 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).<br>• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.<br>• "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.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• 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**<br>The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **Requires in-patient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event. |
| **Results in persistent or significant disability/incapacity**<br>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**<br>Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of |

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

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

**Recording Adverse Events and Serious Adverse Events**

**Adverse Event and Serious Adverse Event Recording**

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the 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 subject'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 subject 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 and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the 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 EDC within 72 hours of the serious adverse event being entered on the Events CRF.

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

**Follow-up of Adverse Event and Serious Adverse Event**

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

**Reporting of Serious Adverse Event**

**Serious Adverse Event Reporting via Electronic Data Collection Tool**

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

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

| A<br>Study # 20210143<br>AMG 451 | Electronic Serious Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

**Reason for reporting this event via fax**

**The Clinical Trial Database (eg. Rave):**

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

**1. SITE INFORMATION**

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number | Fax Number |
|---|---|---|
| | ( ) | ( ) |

**2. SUBJECT INFORMATION**

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

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

**3. SERIOUS ADVERSE EVENT**

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

| Serious Adverse Event diagnosis or syndrome<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report<br>*List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.* | Date Started<br>Day Month Year | Date Ended<br>Day Month Year | Check only if event occurred before first dose of IP | Is event serious? | If serious, enter Serious Criteria code (see codes below) | Relationship<br>Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? | | | | | | | | Outcome of Event<br>-Resolved<br>-Not resolved<br>-Fatal<br>-Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | AMG 451 | | <Device> | | <Device> | | <Device> | | | |
| | | | | | | No✓ | Yes✓ | No✓ | Yes✓ | No✓ | Yes✓ | No✓ | Yes✓ | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |

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

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

| Date Admitted<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

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

| IP/Amgen Device: | | Date of Initial Dose<br>Day Month Year | Prior to, or at time of Event<br>Date of Dose<br>Day Month Year | Dose | Route | Frequency | Action Taken with Product<br>01 Still being Administered<br>02 Permanently discontinued<br>03 Withheld | Lot # and Serial # |
|---|---|---|---|---|---|---|---|---|
| **AMG 451** | ☒ blinded ☐ open label | | | | | | | Lot # _____<br>☐ Unknown<br>Serial # _____<br>☐ Unavailable / Unknown |
| <<IP/Device>> | ☐ blinded ☐ open label | | | | | | | Lot # _____<br>☐ Unknown<br>Serial # |

| A<br>Study # 20210143<br>AMG 451 | Electronic Serious Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

[redacted] ☐ Unavailable / Unknown

| Site Number | Subject ID Number |
|---|---|
| | |

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

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

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

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

| Date (Day Month Year) | Test / Unit | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Test | | | | | | | | | | | |
| | Unit | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

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

| Date (Day Month Year) | Additional Tests | Results | Units |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

| A<br>Study # 20210143<br>AMG 451 | Electronic Serious Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

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

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

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

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

Female subjects should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant during treatment and for 16 weeks after the last dose of **investigational product.**

**Definition of Females of Childbearing Potential**

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

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

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

A postmenopausal female is defined as:

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

**Contraception Methods for Female Subjects**

Highly Effective 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
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

**Collection of Pregnancy Information**

Female Subjects Who Become Pregnant

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

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

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

- Male participants are not required to use forms of contraception during treatment with rocatinlimab. However, male participants should let their female partner know they are in this study.
- In the event a male subject fathers a child during treatment, and for an additional 16 weeks after the last dose of **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 female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

**Collection of Lactation Information**

- Investigator will collect lactation information on any female subject who breastfeeds while taking **investigational product** through 16 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 female subject breastfeeds during the study as described in exclusion criterion 222.
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while

taking **investigational product** through 16 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:** 20210143

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

**2. Contact Information**

**Investigator Name** _____ **Site #** _____

**Phone** (____)_____ **Fax** ( ___ )_____ **Email** _____

**Institution** _____

**Address** _____

**3. Subject Information**

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

**4. Amgen Product Exposure**

| Amgen Product | Dose at time of conception | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

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

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

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

**5. Pregnancy Information**

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

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

Amgen 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:** 20210143

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

### 2. Contact Information

**Investigator Name** _____ **Site #** _____

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

**Institution** _____

**Address** _____

### 3. Subject Information

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

### 4. Amgen Product Exposure

| Amgen Product | Dose at time of breast feeding | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

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

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

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

### 5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

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

## 11.6 Appendix 6. Sample Storage and Destruction

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

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

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

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining, blood samples and any other components from the cells can be located and destroyed. Samples 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 subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

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

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other [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 Other [redacted])Due to Potential Hepatotoxicity**

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

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

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

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

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

**Table 11-3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and [redacted])Due to Potential Hepatotoxicity**

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

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

**Criteria for Rechallenge of Amgen Investigational Product and [redacted])After Potential Hepatotoxicity**

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

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

**Drug-induced Liver Injury Reporting and Additional Assessments**

Reporting

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

- The event is to be reported to Amgen as a serious adverse event immediately and no later than 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate 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 subjects in whom investigational product(s) **and/**or [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 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

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

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize, or the investigational product(s) **and/**or [redacted] has/have been discontinued AND the subject is asymptomatic.

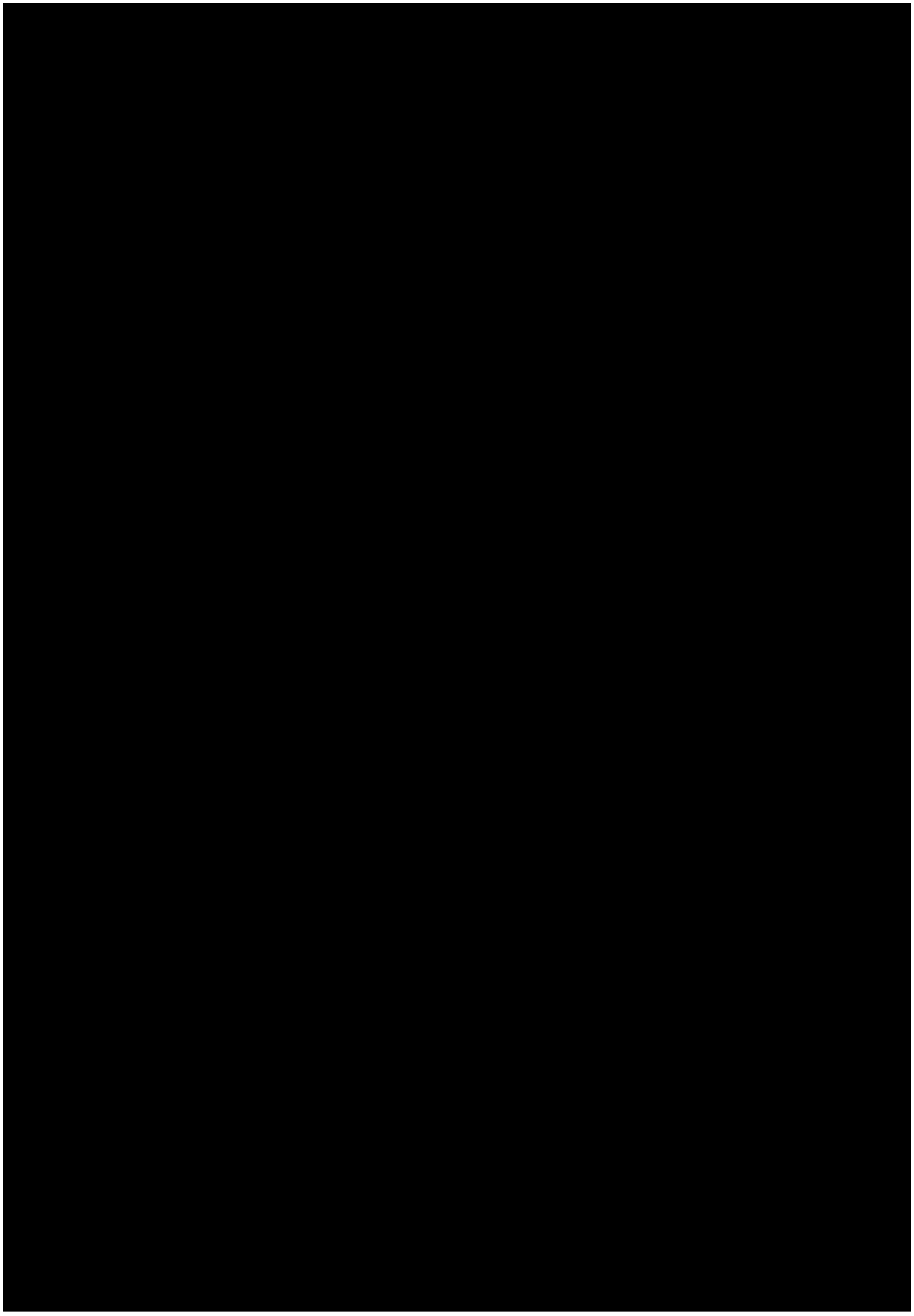
Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (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 subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and**/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.



## 11.9 Appendix 9. Country Specific Requirements

This appendix provides language for country-specific regulatory requirements and other procedures to follow in the execution of the global study in these countries.

The summary of changes outlined below specify requirements for sites and subjects participating in the European Economic Area (EEA).

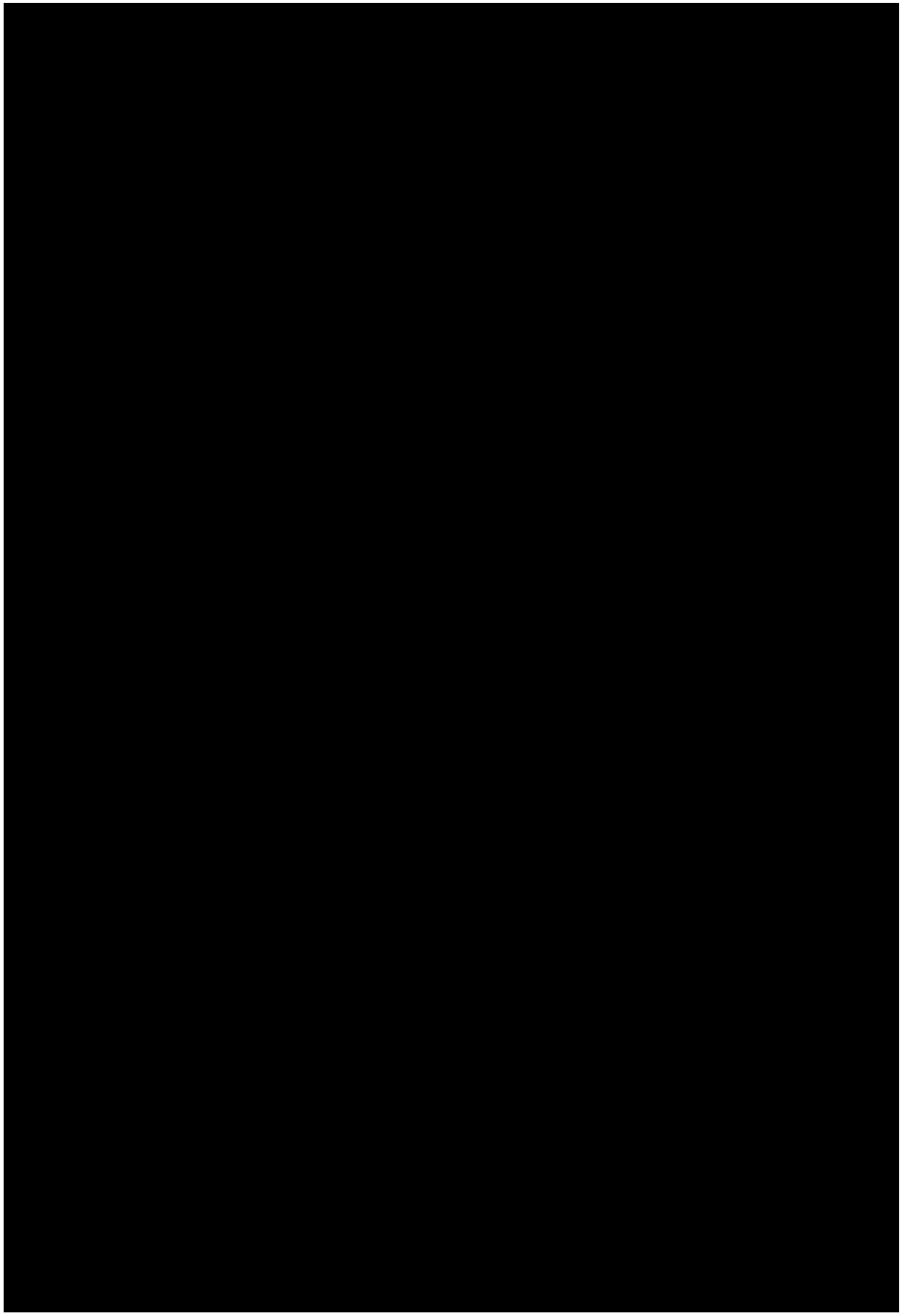
**Table 11-5. European Economic Area Summary of Changes**

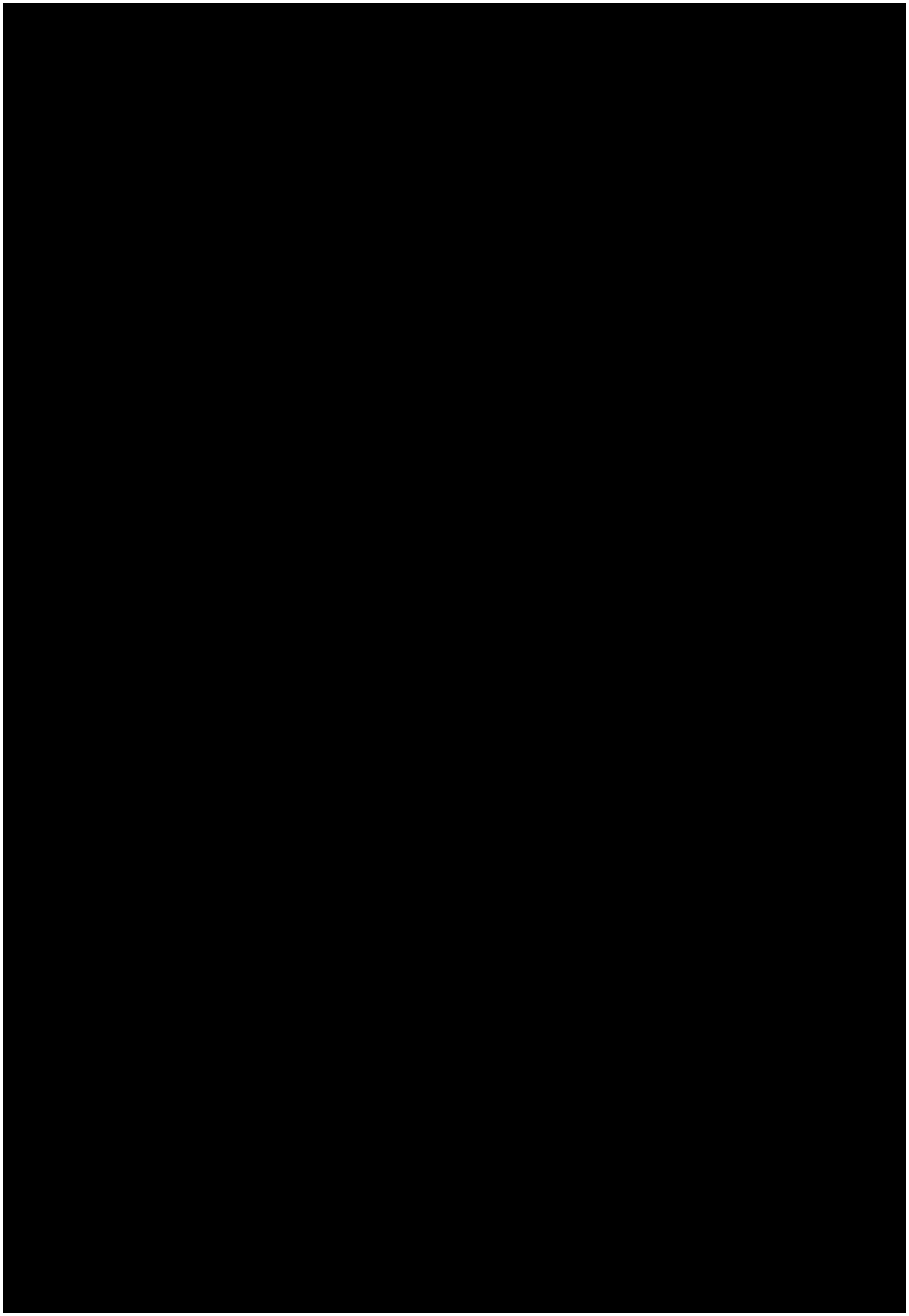
| Protocol Section | Text in Protocol | Text For the EEA |
|---|---|---|
| Section 1.3, Schedule of Activities (SoA), Table 1-1. Schedule of Activities, Footnote **x** | Replaced the following text:<br>[x] For subjects with positive HBsAg and/or HBV core Ab at initial screening. Any additional testing may be performed per investigator's discretion. | With the following text:<br>**[x]** For subjects with positive HB core Ab **without detectable HBV DNA or HBsAg** at initial screening. Any additional testing may be performed per investigator's discretion. |
| Section 5.2, Exclusion Criteria, Criterion no. 234 | Replaced the following text:<br>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 subject with detectable hepatitis B Surface Antigen (HbsAg) and/or antibodies to hepatitis B core. Subjects with detectable HbsAg are required to be virally suppressed with an approved hepatitis B antiviral therapy during the study. | With the following text:<br>**234 Chronic** hepatitis B infection at initial screening, defined as detectable hepatitis B Surface Antigen (HbsAg) or **HBV DNA**. **Subjects with detectable** antibodies to hepatitis B core (anti-HBc) **and negative HBsAg/HBV DNA** are required to **do on-study HBV DNA monitoring**. |

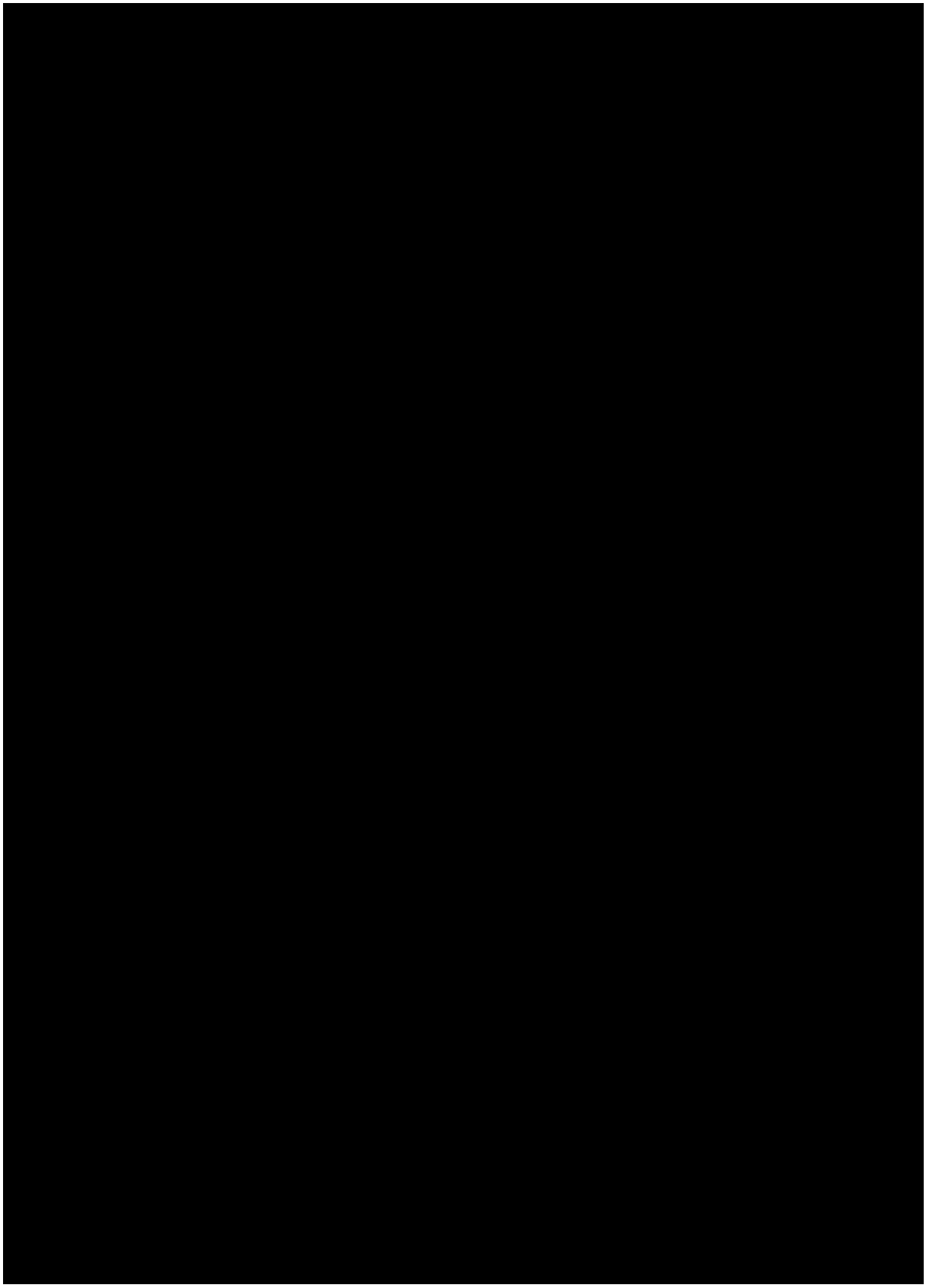
| Protocol Section | Text in Protocol | Text For the EEA |
|---|---|---|
| Section 5.2, Exclusion Criteria, Criterion no. 235 | Replaced the following text:<br>236 Positive or indeterminate QuantiFERON GOLD from central laboratory at initial screening:<br>• Exception: A positive or indeterminate QuantiFERON test is allowed if ALL of the following are present at day 1 prerandomization per Screening TB Risk Assessment Questionnaire provided by Amgen:<br>– No symptoms of tuberculosis (TB)<br>– 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)<br>– No known exposure to a case of active TB after most recent prophylaxis<br>– No evidence of active TB on chest radiograph obtained within 3 months prior to day 1 prerandomization | With the following text:<br>**235 Latent tuberculosis infection as evident by p**ositive or indeterminate QuantiFERON GOLD from central laboratory at day 1 prerandomization per Screening TB Risk Assessment Questionnaire provided by Amgen**.** |
| Section 6.2.2.1, Amgen Investigational Product: Rocatinlimab/Placebo, Paragraph 1, Bullet no. 2 | • Malignancy (excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin) | Deleted the following text:<br>• Malignancy (excluding ~~carcinoma in situ of the cervix, or~~ squamous or basal cell carcinoma of the skin) |

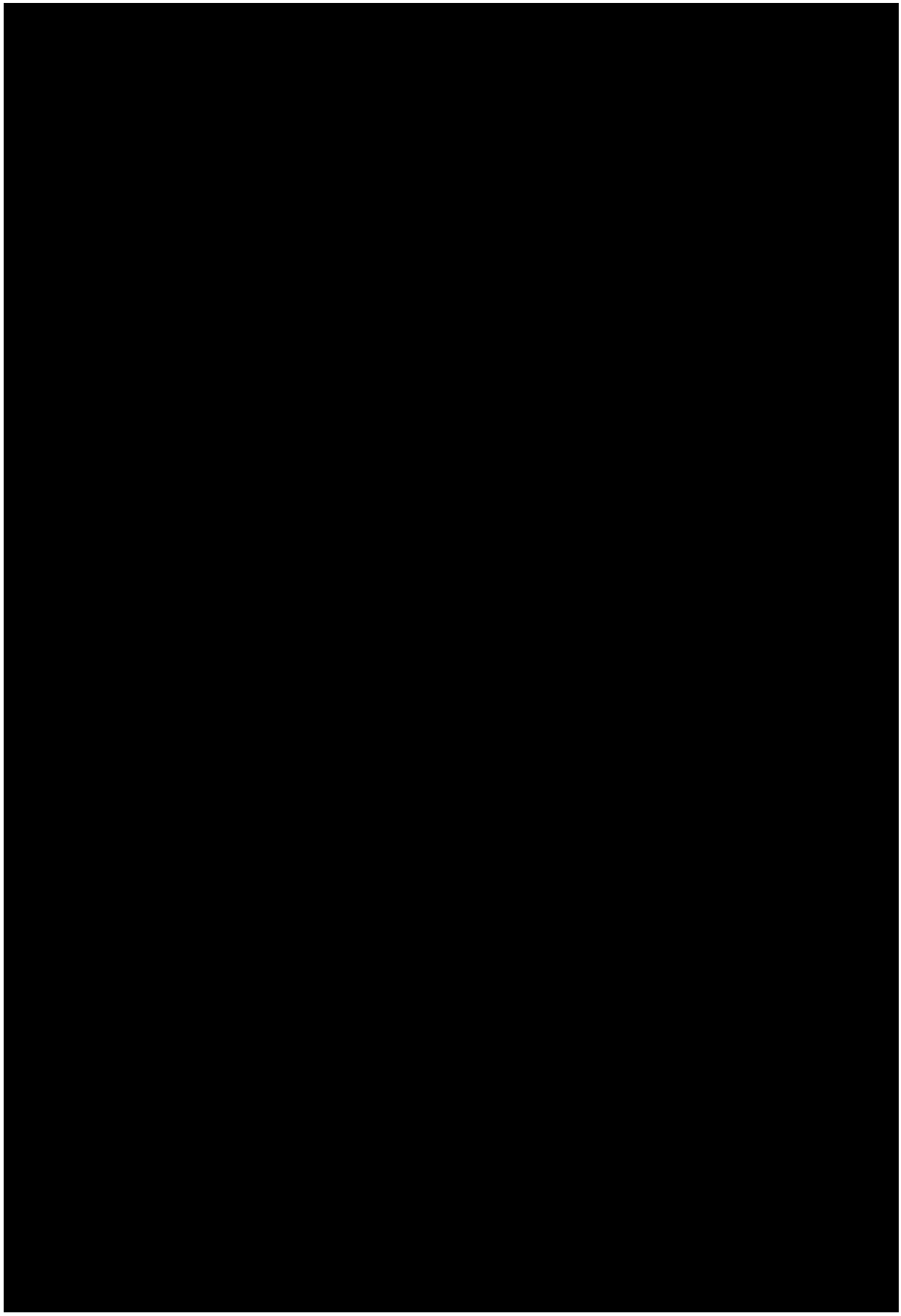
| Protocol Section | Text in Protocol | Text For the EEA |
|---|---|---|
| Section 6.2.2.1, Amgen Investigational Product: Rocatinlimab/Placebo, Paragraph 1, Bullet no. 3 | Replaced the following text:<br>• Opportunistic infection, such as active TB and other infections whose nature or course may suggest an immunocompromised status | With the following text:<br>• Opportunistic infection, such as active TB**, or latent TB, or** other infections whose nature or course may suggest an immunocompromised status |
| Section 8.10.1, Tuberculosis Testing and Tuberculosis Risk Assessment Questionnaire, Screening | Replaced the following text:<br>All subjects must receive QuantiFERON GOLD test from central laboratory at initial screening and Screening TB Risk Assessment Questionnaire must be completed for all subjects as defined in the Schedule of Activities (Section 1.3). Subjects with a positive or indeterminate QuantiFERON GOLD test are ineligible unless specific additional requirements are met (Section 5.2). For subjects with a positive or indeterminate QuantiFERON GOLD test, the radiograph report should be read by a radiologist or per local requirement and the report must be reviewed by the investigator before enrollment. | With the following text:<br>All subjects must receive QuantiFERON GOLD test from central laboratory at initial screening **and Screening TB Risk Assessment Questionnaire must be completed for all subjects** as defined in the Schedule of Activities (Section 1.3). Subjects with a positive or indeterminate QuantiFERON GOLD test are **not** eligible **to enroll** (Section 5.2). |
| Section 8.10.1, Tuberculosis Testing and Tuberculosis Risk Assessment Questionnaire, On-Study, Paragraph 1, Bullet no. 5 | Replaced the following text:<br>• 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 subject should be re-evaluated for signs and symptoms of TB and for prophylactic toxicity within 4 weeks of initiation of prophylactic treatment. | With the following text:<br>• 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 be **discontinued permanently**. |

| Protocol Section | Text in Protocol | Text For the EEA |
|---|---|---|
| [redacted] | [redacted] | Added the following text: [redacted] |









# Approval Signatures

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| Reason for Signing: Management | Name: [redacted]<br>Date of Signature: 29-Nov-2023 22:32:23 GMT+0000 |