

Protocol

A Phase 1 Open-label, Randomized, Parallel-group Study to Assess the Relative Bioavailability of Rocatinlimab (AMG 451) Vial and Prefilled Syringe in Healthy Subjects

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

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INVESTIGATOR AGREEMENT

I have read the protocol entitled “A Phase 1 Open-label, Randomized, Parallel-group Study to Assess the Relative Bioavailability of Rocatinlimab (AMG 451) Vial and Prefilled Syringe in Healthy Subjects” and agree to conduct the study as described herein.

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

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

Signature

Name of Investigator

Date (DD Month YYYY)

Title and Role of Investigator

Institution Name

Address and Telephone Number of Institution

STUDY IDENTIFICATION

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Sponsor's Study Contact	PPD [REDACTED]
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SYNOPSIS

Title of study: A Phase 1 Open-label, Randomized, Parallel-group Study to Assess the Relative Bioavailability of Rocatinlimab (AMG 451) Vial and Prefilled Syringe in Healthy Subjects
Objectives: The primary objective of the study is: - to evaluate the pharmacokinetics (PK) of rocatinlimab given as a single subcutaneous (SC) dose of CCI vial compared to prefilled syringe in healthy subjects. The secondary objective of the study is: - to evaluate the safety, tolerability, and immunogenicity of rocatinlimab after a single SC dose of rocatinlimab in healthy subjects.
Study design: This will be a Phase 1, multi-center, randomized, parallel-group study to investigate the relative bioavailability of rocatinlimab vials and prefilled syringes in healthy subjects. After informed consent is obtained, potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1. On Day 1, subjects will be randomized to receive one of two treatments. Subjects will receive a single SC dose of rocatinlimab (Treatment A or Treatment B) on Day 1 and be confined to the CRU until discharge on Day 14. Subjects will return to the CRU for outpatient visits and an End of Study (EOS) visit on Day 112.
Number of subjects: Approximately CCI subjects will be enrolled in order that approximately CC subjects complete the study.
Diagnosis and main criteria for inclusion: Healthy male or female subjects, 18 to 65 years of age (inclusive), and body mass index of 18 to 32 kg/m ² (inclusive).
Investigational products, dose, and mode of administration: Investigational Medicinal Product: CCI rocatinlimab SC injection Treatment A: CCI vial rocatinlimab SC Treatment B: CCI prefilled syringe rocatinlimab SC
Duration of subject participation in the study: Planned Screening duration: approximately 4 weeks. Planned study duration (Screening to EOS): approximately 20 weeks.
Primary endpoints: Maximum observed serum concentration (C _{max}), area under the serum concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC _{last}), and area under the serum concentration-time curve from time zero to infinity (AUC _{inf}). Secondary endpoints: Secondary endpoints for this study are: treatment-emergent adverse events, serious adverse events, and incidence of CCI

Statistical methods:

The serum PK parameters of rocatinlimab will be calculated using standard noncompartmental methods.

The primary PK parameters are $C_{\max}$, AUC_{last} , and AUC_{inf} for rocatinlimab. Additional PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. An analysis of variance model will be used to analyze log-transformed primary PK parameters. The model assumes fixed effect for treatment. Geometric mean ratios for $C_{\max}$ and AUC values and associated 90% confidence intervals (test/reference) will be estimated. The “reference” treatment for PK analysis will be vial injection, while the “test” treatment will be prefilled syringe injection.

The final safety analysis for the study will be performed at the end of the study. Adverse events will be summarized using descriptive methodology. Each adverse event will be coded using the Medical Dictionary for Regulatory Activities. Endpoints for clinical laboratory tests, electrocardiogram, and vital signs will be summarized.

Additional details will be included in the Statistical Analysis Plan.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	atopic dermatitis
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC _{inf}	area under the serum concentration-time curve from time zero to infinity
AUC _{last}	area under the serum concentration-time curve from time zero to time of last quantifiable concentration
CFR	Code of Federal Regulations
C _{max}	maximum observed serum concentration
COVID-19	coronavirus-2019
CRU	Clinical Research Unit
DILI	drug-induced liver injury
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	end of study
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
MDRD	Modification of Diet in Renal Disease
PK	pharmacokinetic(s)
Q2W	every 2 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected for heart rate using Fridericia's method
SC	subcutaneous
SD	standard deviation
TBL	total bilirubin
Th2	T helper type 2
ULN	upper limit of normal

1. INTRODUCTION

Refer to the Investigator's Brochure (IB)¹ for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational medicinal product (IMP).

1.1. Background

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.² OX40 (CD134) is expressed predominantly on T-cells, including effector cells, shortly after their activation.³ CCI

evaluating the efficacy, safety, and tolerability of repeated doses of rocatinlimab in patients 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 score were observed in all rocatinlimab-treated cohorts versus placebo. In this study, all doses tested were well tolerated with an acceptable adverse event profile.

To date, the efficacy and safety of intravenous (IV) and subcutaneous (SC) rocatinlimab have been evaluated in 5 completed early phase clinical studies and are being evaluated in 8 ongoing studies. A summary of completed and ongoing clinical studies for rocatinlimab is provided in the IB.¹

1.2. Pharmacokinetics

Following single SC administration of rocatinlimab, the mean (standard deviation [SD]) maximum observed serum concentration (C_{max}) is CCI were similar in Japanese and White healthy adults.

The absolute bioavailability of rocatinlimab in Japanese subjects who received SC rocatinlimab was estimated to be CC.

The PK of rocatinlimab was further investigated in patients with moderate-to-severe AD in Study CCI. Following multiple SC doses of rocatinlimab, the concentration-time profile of

serum rocatinlimab increased with increasing doses. The mean (SD) C_{max} after Week 0 and Week 14 in the CCI every 2 weeks (Q2W) group was CCI, respectively. The mean (SD) C_{max} after Week 0 and Week 14 in the CCI Q2W group was CCI, respectively. The PK concentrations appeared to increase dose proportionally. The half-life based on population PK is approximately CCI.

1.3. Study Rationale

The purpose of this study is to determine the relative bioavailability of rocatinlimab vials and rocatinlimab prefilled syringes. The prefilled syringe will provide an alternative device for drug administration and potentially help with patient convenience.

1.4. Benefit-risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB¹ for more information.

1.4.1. Therapeutic Context

1.4.1.1. Key Benefits

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study.

1.4.1.2. Risks

Overall, rocatinlimab has been generally well tolerated and there have been no adverse events with fatal outcomes attributed to rocatinlimab in the completed studies.

CCI
Most of these events were mild or moderate in severity, were nonrecurrent, and mostly observed after administration of the first dose of rocatinlimab. None of these injection-related reactions led to discontinuation of treatment and the majority resolved within 1 to 2 days after dosing with or without administration of antipyretics. Other common adverse events were headache, injection-site reactions, and aphthous ulcer, reported in 8.8%, 5.0%, and 6.9% of subjects, respectively.

CCI

Approximately [CCI] received at least 1 dose of rocatinlimab in the completed studies, including healthy subjects and patients with plaque psoriasis, ulcerative colitis, and AD.

As further described in this protocol, eligibility criteria have been implemented to exclude subjects vulnerable to acute allergic reactions and infections. All subjects will be observed after IMP administration and will be monitored throughout the study with physical examination, laboratory assessments (hematology, urinalysis, and chemistry panels), electrocardiogram (ECG), vital signs monitoring, and standard adverse event and serious adverse event reporting.

Refer to the IB¹ for further data on rocatinlimab.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the PK of rocatinlimab given as a single SC dose of [CCI] vial compared to prefilled syringe in healthy subjects.

The secondary objective of the study is:

- to evaluate the safety, tolerability, and immunogenicity of rocatinlimab after a single SC dose of rocatinlimab in healthy subjects.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

- C_{max}
- area under the serum concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last})
- AUC from time zero to infinity (AUC_{inf}).

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- treatment-emergent adverse events
- serious adverse events
- [CCI]

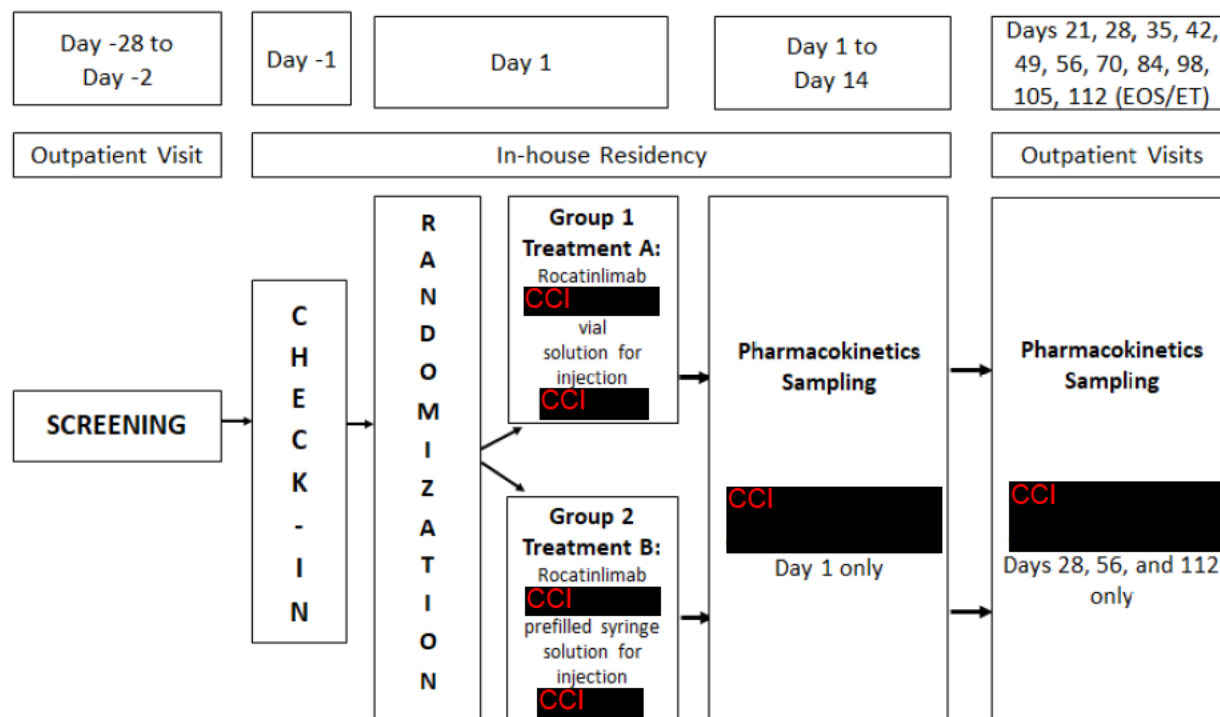
3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase 1, multi-center, randomized, parallel-group study to investigate the relative bioavailability of rocatinlimab vials and prefilled syringes in healthy subjects. After informed consent is obtained, potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the dose administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1. On Day 1, subjects will be randomized to receive one of two treatments.. Subjects will receive a single SC dose of rocatinlimab (Treatment A or Treatment B) on Day 1 and be confined to the CRU until discharge on Day 14. Subjects will return to the CRU for outpatient visits on Days 21, 28, 35, 42, 49, 56, 70, 84, 98, and 105 and an End of Study (EOS) visit on Day 112.

An overview of the study design is shown in [Figure 1](#).

Figure 1: Study Schematic



The estimated glomerular filtration rate will be determined by the Modification of Diet in Renal Disease (MDRD) formula⁷ and will be rounded and presented as the nearest whole number:

MDRD formula (mL/min/1.73m²) = 175 x (serum creatinine)^{-1.154} x (age)^{-0.203} x (0.742 if female) x (1.212 if African American)

The total duration of study participation for each subject (from Screening through EOS visit) is anticipated to be approximately 20 weeks.

The start of the study is defined as the date the first enrolled subject signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in [Appendix 7](#).

3.2. Discussion of Study Design

This study is designed to evaluate the relative bioavailability of the rocatinlimab vial compared to rocatinlimab prefilled syringes. This study will be open-label because the study endpoints are not considered subjective.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

3.3. Selection of Doses in the Study

The rocatinlimab dose selected in this study is a [REDACTED] single dose. The ongoing [REDACTED] studies are evaluating [REDACTED] every 4 weeks (Q4W) with a [REDACTED] loading dose at Week 2, and [REDACTED] Q4W with a [REDACTED] loading dose at Week 2, in patients with moderate-to-severe AD.

In the clinical development studies, doses were tested in the range of [REDACTED] IV and 1 to [REDACTED] Q2W SC. All the tested doses were found to be well tolerated.

Hence, a [REDACTED] single dose, the highest dose evaluated in [REDACTED] studies, is selected for this study which is expected to be safe and well tolerated.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria prior to enrollment unless otherwise stated:

1. Subject has provided informed consent before initiation of any study-specific activities/procedures.
2. Healthy male or female subjects, between 18 and 65 years of age (inclusive) at the time of Screening.
3. In good health, determined by no clinically significant findings from medical history, physical examination (performed at Check-in), 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [e.g.,

suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).

4. Body mass index between 18 and 32 kg/m² (inclusive) at the time of Screening.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria prior to enrollment unless otherwise stated. A repeat of clinical laboratory assessments and safety assessments that are out of range will be allowed to confirm subject ineligibility prior to disqualification:

1. History or evidence, at Screening or Check-in, of clinically significant disorder, condition, or disease not otherwise excluded that, in the opinion of the Investigator (or designee), would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
2. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.
3. A QT interval corrected for heart rate using Fridericia's method (QTcF) > 450 msec in male subjects or > 470 msec in female subjects or history/evidence of long QT syndrome at Screening or Check-in.
4. 2nd degree atrioventricular block, 3rd degree atrioventricular block, or any clinically significant ECG abnormality at Screening or Check-in.
5. Systolic blood pressure > 140 mmHg or < 90 mmHg, or diastolic blood pressure > 90 mmHg, or pulse rate > 100 bpm (based on vital signs measurement) at Screening or Check-in. Subjects with out-of-range values that are not clinically significant (as determined by the Investigator) may have the test repeated once during Screening or at Check-in (within 1 hour of original assessment) and the subject may be enrolled if a repeated value is within normal range.
6. History of hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee). Subjects with seasonal allergies will be permitted.
7. Poor peripheral venous access.
8. Estimated glomerular filtration rate less than 70 mL/min/1.73 m² as calculated by the MDRD equation at Screening. Out-of-range laboratory values may be repeated at Screening and/or Check-in.
9. Alanine aminotransferase or aspartate aminotransferase > 1.5 times the upper limit of normal at Screening or Check-in. Out-of-range laboratory values may be repeated at Screening and/or Check-in.

10. Positive hepatitis B or hepatitis C panel (including positive hepatitis B surface antigen [HBsAg] and/or positive hepatitis C antibody) and/or positive human immunodeficiency virus test at Screening. Subjects whose results are compatible with prior hepatitis B vaccination (positive hepatitis B surface antibody, negative hepatitis B core antibody, negative HBsAg) or prior infection (positive hepatitis B core antibody, positive hepatitis B surface antibody, negative HBsAg) may be included.
11. Subjects who have received live vaccines within 5 weeks prior to Screening, or plan to receive live vaccines within 90 days after administration of an investigational product. Inactive vaccination (e.g., nonlive or nonreplicating agent), including coronavirus-2019 (COVID-19) vaccination, is allowed.
12. History of latent tuberculosis or active chronic, recurrent, 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 Screening.
13. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) before Check-in, excluding the following:
 - a. Acetaminophen (paracetamol) (up to 2 g per day) for analgesia will be allowed.
 - b. Hormonal contraception listed in [Appendix 3](#) will be allowed.
 - c. Hormone replacement therapy (e.g., estrogen) and hormonal contraceptives will be allowed.
14. All herbal medicines (e.g., St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to Check-in, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
15. History of alcoholism or regular alcohol consumption of > 21 units per week for males and > 14 units per week for females or drug/chemical abuse within 1 year prior to Check-in. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
16. Alcohol consumption from 36 hours prior to Check-in.
17. Use of tobacco- or nicotine-containing products within 6 months prior to Check-in.
18. Positive test for illicit drugs, cotinine (tobacco or nicotine use) at Screening or Check-in, and positive alcohol test at Check-in.
19. Female subjects with a positive pregnancy test at Screening or Check-in.
20. Female subjects lactating/breastfeeding or who plan to breastfeed during the study through the EOS visit.
21. Unwilling to adhere to contraceptive requirements through the EOS visit (see [Appendix 3](#)).

22. Unwilling to abstain from sperm donation and ovum donation through the EOS visit (see [Appendix 3](#)).
23. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
24. Male subjects with a pregnant partner or partner planning to become pregnant while the subject is on study through the EOS visit.
25. Subject has received a dose of an investigational drug within the past 90 days or 5 half-lives, whichever is longer, prior to Check-in.
26. Have previously completed or withdrawn from this study or any other study investigating rocatinlimab or have previously received the IMP.
27. Donation of blood within 90 days prior to Check-in, plasma within 2 weeks prior to Check-in, or platelets within 6 weeks prior to Check-in.
28. Unwilling to refrain from new or excessively strenuous exercise from 7 days before Check-in until the EOS visit.
29. Unwilling to abide with study restrictions.
30. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

4.3. Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study because they do not meet eligibility requirements. A minimal set of screen failure information may be collected, including demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once.

4.4. CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

4.5. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn from dosing if any of the following criteria are met:

- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal.

If a subject is withdrawn from dosing, the Sponsor (or designee) will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic Case Report Form (eCRF). If a subject is withdrawn, efforts will be made to perform all EOS assessments, if possible ([Appendix 7](#)). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the CRU unless the subject is discharged due to a condition that will put staff or other subjects at risk (such as COVID-19, other infection, or behavioral issues). The Investigator (or designee) may also request that the subject return for early termination procedures or for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their Adverse Events, Adverse Device Effects, Serious Adverse Events, or until the unresolved Adverse Events, Adverse Device Effects, Serious Adverse Events are judged by the Investigator (or designee) to have stabilized.

Subjects who are withdrawn for reasons not related to study drug may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of Adverse Events/Serious Adverse Events thought to be related to the study drug will generally not be replaced.

4.6. Study Termination

- The Sponsor 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 Good Clinical Practice. Both the Sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The Investigator is to notify the Institutional Review Board (IRB) or Ethics Committee (EC) in writing of the study's completion or early termination and send a copy of the notification to the Sponsor. The Sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply IMP and by what mechanism, after termination of the study.

- In addition, the study may be terminated by the Sponsor at any time and for any reason. If the Sponsor decides to terminate the study, they will inform the Investigator as soon as possible.

5. STUDY TREATMENTS

Study treatment is defined as any investigational product, non-investigational product, placebo, or medical device intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

5.1. Investigational Product

The IMP will be supplied by the Sponsor. Detailed information regarding the storage, preparation, destruction, and administration of the IMP will be provided. The IMPs used in this study are summarized in [Table 1](#).

All supplies of IMP will be stored in accordance with the manufacturer's instructions. Until dispensed to the subjects, the IMPs will be stored at the study site in a location that is locked with restricted access.

At the UK site, the IMP will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificates of Analysis. A Certificate of Release authorized by a Qualified Person in the European Union will also be issued for the IMP. A declaration of Good Manufacturing Practice equivalence issued by a Qualified Person in the European Union will also be issued for the IMP.

The IMP will be provided in vials and prefilled syringes and stored according to manufacturer's instructions.

5.2. Investigational Product Administration

Table 1: Investigational Products

Study Treatment Name	Investigational Medicinal Product: Rocatinlimab Treatment A	Investigational Medicinal Product: Rocatinlimab Treatment B
	CCI [REDACTED] vial solution for injection	CCI [REDACTED] prefilled syringe solution for injection
Unit Strength and Formulation	CCI [REDACTED]	

Dosage Level	CCI on Day 1
Route of Administration	Subcutaneous injection
Accountability	The quantity administered, date administered, and lot number of investigational product are to be recorded on the appropriate forms.
Dosing Instructions	The Investigator/designee will administer the treatment after the completion of all predose procedures. The subcutaneous injection will be administered in the abdomen.

5.3. Treatment of Overdose

The effects of overdose of rocatinlimab are not known. In case of overdose, consultation with the Medical Monitor is recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage, and to discuss further management of the subject.

5.4. Medical Devices

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 (e.g., syringes, sterile needles) that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

The rocatinlimab prefilled syringe is a single-use disposable, handheld manual injection device for fixed dose SC injection of CCI rocatinlimab in a CCI deliverable volume.

5.5. 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 rocatinlimab provisioned and/or repackaged/modified by Amgen:

Any product complaint(s) associated with rocatinlimab vials or rocatinlimab prefilled syringes supplied by Amgen are to be reported.

5.6. Randomization

This is a randomized, parallel-group study. Subjects will be randomized (1:1) into 1 of 2 treatment groups based on the study randomization scheme developed and approved by the Study Statistician.

5.7. Blinding

This is an open-label study.

5.8. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- When subjects are dosed at the site, they will receive rocatinlimab directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the CRU will be recorded in the source documents and recorded on the eCRF.
- At each dosing occasion, a predose and postdose inventory of IMP will be performed.

5.9. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of rocatinlimab received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Individual site procedures for the disposal of syringes will be followed. Any unused assembled unit doses will be retained until completion of the study.

5.10. Sample Retention

Sufficient IMP samples will be randomly selected from the supply provided by the Sponsor and retained by the study site(s) to meet the retention requirements described in United States Title 21 Code of Federal Regulations 320.38 and 320.63.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the EOS visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Acetaminophen (paracetamol) (2 g/day), hormone replacement therapy, or oral, implantable, transdermal, injectable, or intrauterine contraceptives are acceptable concomitant medications. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for treatment

of an adverse event/serious adverse event. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

6.2. Diet

Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations. Water intake will not be restricted. While confined at the study site, subjects will receive a diet provided by the site at scheduled times that do not conflict with other study-related activities. No outside food or beverage will be permitted during confinement.

Consumption of alcohol will not be permitted from 36 hours prior to Check-in on Day -1, and alcohol intake will be limited to a maximum of 1 unit/day on all other days, while not in the CRU, from Screening through the EOS visit.

6.3. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 6 months prior to Check-in until the EOS visit.

6.4. Exercise

Subjects are required to refrain from new or excessively strenuous exercise from 7 days before Check-in until the EOS visit. Subjects will otherwise maintain their normal level of physical activity during this time (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.5. Blood Donation

Subjects are required to refrain from donation of blood from 90 days prior to Check-in, plasma from 2 weeks prior to Check-in, and platelets from 6 weeks prior to Check-in until 3 months after the EOS visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- predose clinical laboratory assessments
- predose/trough PK blood samples
- CCI [REDACTED]

- dosing
- PK blood samples (postdose)
- postdose safety assessments (ECGs will be scheduled before vital signs measurements)
- any other procedures.

Where activities at a given timepoint coincide, consideration must be given to ensure that the following order of activities is maintained: ECGs, vital signs, and safety laboratory assessments.

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for rocatinlimab will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in [Appendix 7](#). Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

Any blood sample collected according to the Schedule of Assessments ([Appendix 7](#)) 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.

7.1.2. Analytical Methodology

Serum concentrations of rocatinlimab will be determined using validated analytical procedures. Specifics of the analytical method will be provided in a separate document.

7.2. CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

7.3. Safety and Tolerability Assessments

7.3.1. Adverse Events, Adverse Device Effects, and Serious Adverse Events: Time Period and Frequency for Collecting and Reporting Safety Event Information

Adverse event definitions, assignment of severity and causality, and procedures for reporting Adverse Events, Adverse Device Effects, and Serious Adverse Events are detailed in [Appendix 1](#).

The condition of each subject will be monitored from enrollment to EOS. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report Adverse Events, Adverse Device Effects, and Serious Adverse Events occurring at any other time during the study.

Adverse Events

The adverse event grading scale to be used in this study is described in [Appendix 1](#).

The Investigator is responsible for ensuring that all non-serious adverse events observed by the Investigator or reported by the subject (whether reported by the subject voluntarily or upon questioning, or noted on physical examination) from initiation of study treatment through the EOS visit are recorded/reported using the appropriate eCRF.

Adverse Device Effects

In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

An adverse device effect is any adverse event related to the use of a combination product (definition of combination product is provided in [Appendix 1](#)) or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures.

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 ICF through 30 days after the last dose of study treatment or the EOS visit (whichever is later) are reported using the

appropriate eCRF and reported on the paper-based Serious Adverse Event Report Form (described in [Appendix 1](#)).

All serious adverse events will be collected, recorded, and reported to the Sponsor immediately and no later than 24 hours of the Investigator's knowledge of the event. The Investigator will submit any updated Serious Adverse Event data to the Sponsor immediately and no later than 24 hours of it being available.

Serious Adverse Events After the Protocol-Required Reporting Period

After EOS, 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 (regardless of causality), 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 Sponsor's safety database as clinical trial cases and handled accordingly based on relationship to IMP.

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.

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 nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

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, where possible, until resolution, stabilization, until the event is otherwise explained, or the subject is Lost to Follow-up. This will be completed at the Investigator's (or designee's) discretion.

All new information for previously reported serious adverse events must be sent to Amgen immediately and no later than 24 hours following knowledge 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 eCRF.

Regulatory Reporting Requirements for Serious Adverse Events

If a subject is permanently withdrawn from investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to the Sponsor.

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/ECs, 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 (e.g., summary or listing of serious adverse events) from the Sponsor will file it along with the IB and will notify the IRB or EC, if appropriate according to local requirements.

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 event reports sent to regulatory authorities in accordance with local requirements.

Amgen will prepare a single Development Safety Update Report (also referred to as Annual Safety Report in the European Union) for the Amgen investigational product. To ensure that consolidated safety information for the study is provided, this single Development Safety Update Report will also include appropriate information on any other investigational products used in the clinical study, if applicable.

Safety Monitoring Plan

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

Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and pregnancies in female partners of male subjects will be collected after the start of the study treatment and until EOS.

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 [Appendix 4](#). Amgen Global Patient Safety will follow-up with the Investigator regarding additional information that may be requested.

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

Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at Screening and at Day -1 before initiation of IMP for females.

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 3](#)). Refer to [Appendix 3](#) for contraceptive requirements.

A pregnancy test should be performed at the end of the period of relevant systemic exposure after discontinuing investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s).

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

Further details regarding pregnancy and lactation are provided in [Appendix 4](#).

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in [Appendix 7](#). Clinical laboratory evaluations are listed in [Appendix 2](#).

The Investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the eCRF. 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 judgement) 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.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol test at the times indicated in the Schedule of Assessments in [Appendix 7](#). For all female subjects, a pregnancy test and follicle-stimulating hormone screen for

postmenopausal women will be performed at the times indicated in the Schedule of Assessments in [Appendix 7](#).

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in [Appendix 7](#). Vital signs will be performed predose and at the end of a postdose monitoring period. Vital signs may also be performed at other times if judged to be clinically appropriate.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

7.3.4. 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in [Appendix 7](#). Single 12-lead ECGs will be repeated twice, and an average taken of the 3 readings, if either of the following criteria apply:

- QTcF is >500 ms
- QTcF change from the baseline (predose) is >60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG and initiate further work-up or intervention as necessary.

7.3.5. Physical Examination

Physical examination will be performed and will include a neurological examination (breast, rectal, and genital examination are not required). Neurologic examination will include evaluation of mental status/cognition/mood/affect, gross and fine motor, sensory, cranial nerves, coordination, and deep tendon reflexes. Physical examination findings should be recorded on the appropriate eCRF (e.g., medical history, treatment-emergent adverse event). Physical examinations will be performed at the timepoints specified in the Schedule of Assessments in [Appendix 7](#).

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Approximately CCI subjects will be randomized into 2 treatment groups CCI per group).

Assuming CCI

Assuming CCI

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of rocatinlimab and have evaluable PK data.

8.2.2. Safety Population

The safety population will include all subjects who received at least 1 dose of rocatinlimab and have at least 1 postdose safety assessment.

8.3. Pharmacokinetic Analyses

The serum PK parameters of rocatinlimab will be calculated using standard noncompartmental methods.

The primary PK parameters are C_{max} , AUC_{last} , and AUC_{inf} for rocatinlimab. Additional PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. An analysis of variance will be used to analyze log-transformed primary PK parameters. The model assumes fixed effect for treatment. Geometric mean ratios for C_{max} and AUC values and associated 90% confidence intervals (test/reference) will be estimated. The “reference” treatment for PK analysis will be vial injection, while the “test” treatment will be prefilled syringe injection.

Additional parameters may be calculated. Specific details will be presented in the Statistical Analysis Plan for this study.

8.4. Safety Analysis

The number and percentage of subjects reporting any adverse events will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s),

and significant treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

Endpoints for clinical laboratory tests, ECG, and vital signs will be summarized.

8.5. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

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10. APPENDICES

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events, Adverse Device Effects, Serious Adverse Events

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device, or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, 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 (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

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

Definition of Adverse Device Effect

Adverse Device Event Definition
The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen and non-Amgen medical devices provided for use in the study (see Section 5.4 for the list of medical devices).
Events Meeting the Adverse Device Event Definition An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include, but are not limited to, adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device. A combination product is a product composed of any combination of a drug, a device, and a biological product. Each drug, device, and biological product included in a combination product is referred to as a “constituent part” of the combination product.

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 available documentation (e.g., 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 electronic Case Report Form (eCRF). - The Investigator must assign the following 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(s), and/or noninvestigational product(s)/auxiliary medicinal product(s); - Assessment of seriousness; - Severity (or toxicity defined below); - Assessment of relatedness to the investigational product(s) and/or study-mandated procedures; - 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 appropriate eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the appropriate eCRF 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 the Sponsor.
- 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.	
Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated, usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	Discomfort enough to cause interference with usual activity causing discomfort but poses no significant or permanent risk of harm to the subject. Usually alleviated with additional specific therapeutic intervention.
SEVERE ^a	Incapacitating with inability to work or interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
^a An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.	
Assessment of Causality	
• The Investigator is obligated to assess the relationship between investigational product(s), device(s), study-required activity and/or procedure(s) and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The Investigator will use clinical judgment to determine the relationship.	

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the Investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- 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.
- 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 the Sponsor 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 non-investigational product(s)/auxiliary medicinal product(s) because of a serious adverse event, this information must be submitted to the Sponsor.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper Serious Adverse Event Report Form

- Facsimile transmission of the Serious Adverse Event Report Form (see [Figure 2](#)) is the preferred method to transmit this information.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Once the study has ended, serious event(s) suspected to be related to investigational product will be reported to Amgen immediately and no later than 24 hours if the Investigator becomes aware of a serious adverse event. The Investigator should use the paper-based Serious Adverse Event Report Form to report the event.
- The Safety Management Plan will delineate the processes and responsibilities for serious adverse event reporting.

Recording Adverse Device Events

Adverse Device Effects: Recording, Evaluating, and Reporting

- Any adverse event resulting from an adverse device effect that occurs during the study will be documented in accordance with the Investigator's normal clinical practice, and on the Event eCRF page.
- It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Figure 2: Sample Serious Adverse Event Report Form

US Site Only

AMGEN Protocol # 20220015 Supplier Protocol # 8524870 AMG 451	Clinical Trial Serious Adverse Event Report – Phase 1–4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	☐ New ☐ Follow-up
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PPD

1. SITE INFORMATION											
Site Number	Investigator				Country		Date of Report				
							Day Month Year				
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					
3. SERIOUS ADVERSE EVENT - Information in this section must also be entered on the Serious Adverse Event Summary CRF											
Provide the date the Investigator became aware of this Serious Adverse Event information: Day Month Year											
Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event <i>List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.</i>	Date Started		Date Ended		Check only if event occurred before first dose of IP	Enter Serious Adverse Code (see codes below)	Relationship 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	Check only if event is related to study procedure eg. biopsy
	Day Month Year		Day Month Year				If yes see section 10 Rocatinimab Rocatinimab prefilled syringe			01 Resolved 02 Not resolved 03 Fatal 04 Unknown	
Serious Criteria: 01 Fatal 03 Required hospitalization 05 Persistent or significant disability /incapacity 07 Other medically important serious event 02 Immediately life-threatening 04 Prolonged hospitalization 06 Congenital anomaly / birth defect											
4. HOSPITALIZATION											
Was subject hospitalized or was a hospitalization prolonged due to this event? ☐ No ☐ Yes. If yes, please complete date(s):					Date Admitted			Date Discharged			
					Day Month Year			Day Month Year			
5. INVESTIGATIONAL PRODUCT (IP)											
	Initial Start Date		Prior to, or at time of Event				Action Taken with Product		Lot # and Serial #		
	Day Month Year		Date of Dose		Dose	Route	Frequency	01 Still being Administered 02 Permanently discontinued 03 Withheld		Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown	
Rocatinimab ☐ Blinded X Open Label			Day Month Year								Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown
Rocatinimab Prefilled Syringe ☐ Blinded X Open Label			Day Month Year								Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown

Site Number				Subject ID Number													
6. CONCOMITANT MEDICATIONS (eg, chemotherapy)								Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:									
Medication Name(s)	Start Date			Stop Date			Co-suspect		Continuing		Dose	Route	Freq.	Treatment Me			
	Day	Month	Year	Day	Month	Year	No✓	Yes✓	No✓	Yes✓				No✓	Yes✓		
7. RELEVANT MEDICAL HISTORY (include dates, allergies and any relevant prior therapy)																	
8. RELEVANT LABORATORY VALUES (include baseline values) Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:																	
Date	Test																
	Unit																
Day	Month	Year															
9. OTHER RELEVANT TESTS (diagnostics and procedures) Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:																	
Date	Additional Tests					Results					Units						
Day	Month	Year															

AMGEN Protocol # 20220015 Supplier Protocol # 8524870 AMG 451	Clinical Trial Serious Adverse Event Report – Phase 1–4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	☐ New ☐ Follow-up
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	Site Number	Subject ID Number	
10. CASE DESCRIPTION (Provide narrative details of events listed in section 3) For each event in section 3, where relationship=Yes, please provide rationale.			
Signature of Investigator or Designee		Title	Date
<i>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.</i>			

FOR INTERNAL USE ONLY – Note for Case Management/ISOs: DO NOT send queries to the clinical site. Please direct all follow-up queries related to this SAE to PPD

AMGEN Protocol # 20220015 Supplier Protocol # 8524870 AMG 451	Clinical Trial Serious Adverse Event Report – Phase 1–4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	☐ New ☐ Follow-up
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PPD																																																																																													
1. SITE INFORMATION																																																																																													
Site Number			Investigator				Country			Date of Report Day Month Year																																																																																			
			Reporter				Phone Number () ()			Fax Number () ()																																																																																			
2. SUBJECT INFORMATION																																																																																													
Subject ID Number			Age at event onset				Sex ☐ F ☐ M		Race		If applicable, provide End of Study date																																																																																		
3. SERIOUS ADVERSE EVENT - Information in this section must also be entered on the Serious Adverse Event Summary CRF																																																																																													
Provide the date the Investigator became aware of this Serious Adverse Event Information: Day Month Year																																																																																													
Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event <i>List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.</i>		Date Started Day Month Year		Date Ended Day Month Year		Check only if event occurred before first dose of IP Enter Serious Adverse Code (see codes below)	Relationship 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 01 Resolved 02 Not resolved 03 Fatal 04 Unknown		Check only if event related to study procedure eg, biopsy																																																																																
							If yes see section 10 Rocatinimab Rocatinimab prefilled syringe <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>No</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>Yes</td><td>No</td><td>Yes</td> </tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </table>							No	Yes	No	Yes	No	Yes	No	Yes	No	Yes																																																																						
No	Yes	No	Yes	No	Yes	No	Yes	No	Yes																																																																																				
Serious 01 Fatal Criteria: 02 Immediately life-threatening 03 Required hospitalization 04 Prolonged hospitalization 05 Persistent or significant disability/incapacity 06 Congenital anomaly / birth defect 07 Other medically important serious event																																																																																													
4. HOSPITALIZATION																																																																																													
Was subject hospitalized or was a hospitalization prolonged due to this event? ☐ No ☐ Yes. If yes, please complete date(s):						Date Admitted Day Month Year				Date Discharged Day Month Year																																																																																			
5. INVESTIGATIONAL PRODUCT (IP)																																																																																													
		Initial Start Date		Prior to, or at time of Event				Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld		Lot # and Serial #																																																																																			
		Date of Dose		Dose		Route						Frequency																																																																																	
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Rocatinimab ☐ Blinded X Open Label										Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown																																																																																			
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AMGEN Protocol # 20220015 Supplier Protocol # 8524870 AMG 451	Clinical Trial Serious Adverse Event Report – Phase 1–4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	☐ New ☐ Follow-up
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			Site Number			Subject ID Number												
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant Medications? ☐ No ☐ Yes, If yes, please complete:																		
Medication Name(s)		Start Date			Stop Date			Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med			
		Day	Month	Year	Day	Month	Year	No✓	Yes✓	No✓	Yes✓				No✓	Yes✓		
7. RELEVANT MEDICAL HISTORY (include dates, allergies and any relevant prior therapy)																		
8. RELEVANT LABORATORY VALUES (include baseline values) Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:																		
Date	Test																	
	Unit																	
Day	Month	Year																
9. OTHER RELEVANT TESTS (diagnostics and procedures) Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:																		
Date		Additional Tests								Results				Units				
Day	Month	Year																

AMGEN Protocol # 20220015 Supplier Protocol # 8524870 AMG 451	Clinical Trial Serious Adverse Event Report – Phase 1–4 <i>Notify Amgen Within 24 Hours of knowledge of the event</i>	☐ New ☐ Follow-up
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	Site Number	Subject ID Number	
10. CASE DESCRIPTION (Provide narrative details of events listed in section 3) For each event in section 3, where relationship=Yes, please provide rationale.			
Signature of Investigator or Designee		Title	Date
<i>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.</i>			

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Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Direct bilirubin ^a Gammaglutamyl transferase Glucose Indirect bilirubin ^a Inorganic phosphate Potassium Sodium Total bilirubin ^a Total CO ₂ Total protein Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential (% and absolute): Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Serology ^b :	Drug screen:	Hormone panel – females only:
Hepatitis B surface antibody Hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV1 and HIV2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/cannabinoids Cotinine test Alcohol test ^c	Follicle-stimulating hormone ^{b, d} Serum pregnancy test (human chorionic gonadotropin) ^e Urine pregnancy test ^e
		Hepatotoxicity only Hepatotoxicity only: International normalized ratio (INR) ^f Prothrombin time ^f
		Other tests: Estimated glomerular filtration rate (eGFR) ^g

^a Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.

^b Only analyzed at Screening.

^c Only analyzed at Check-in.

^d Follicle-stimulating hormone testing to be performed in all female subjects.

^e Performed in serum at Screening and in urine at all other times for all females. A positive urine pregnancy test will be confirmed with a serum pregnancy test and may be further assessed with a quantitative beta human chorionic gonadotropin.

^f International normalized ratio and prothrombin time will be tested if hepatotoxicity is suspected, per guidelines presented in [Appendix 6](#).

^g Estimated glomerular filtration rate will be calculated by the Modified Renal Disease (MDRD) equation.

MDRD formula (mL/min/1.73m²) = 175 x (serum creatinine)^{-1.154} x (age)^{-0.203} x (0.742 if female) x (1.212 if African American)⁸

Appendix 3: Contraception Requirements

All subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they conceive a child during treatment through the end of study (EOS) visit.

Additional medications given during the study may alter the contraceptive requirements. The Investigator must discuss these contraceptive changes with the subject.

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

- **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
- **Postmenopausal subjects:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.
- **Postmenopausal female partners:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason. Confirmatory FSH levels will not be required. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease, or polycystic ovarian disease or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators.

Fertile male: a male that is considered fertile after puberty.

Contraception Requirements

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential who are sexually active with a male partner must be willing to use 2 methods (1 primary and 1 secondary method) of birth control from the time of signing the Informed Consent Form (ICF) through the EOS visit.

Primary methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill associated with inhibition of ovulation (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 3 months prior to the Screening visit:
 - Bilateral tubal ligation with confirmation of surgical success
 - Regulatory approved method of hysteroscopic bilateral tubal occlusion with confirmation of occlusion of the fallopian tubes
- hormonal implant
- hormonal or non-hormonal intrauterine device
- vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success, and the sole partner for the female subject).

Secondary (barrier) methods of contraception include:

- male condom with spermicide
- female condom with spermicide
- over-the-counter sponge with spermicide
- cervical cap with spermicide (as prescribed)
- diaphragm with spermicide (as prescribed).

Female subjects should refrain from donation of ova from Check-in (Day -1) through the EOS visit.

Male Subjects

Male subjects with partners of childbearing potential must use a male barrier method of contraception (i.e., male condom with spermicide) and ensure that their female partner uses a second method of acceptable contraception from Check-in through the EOS visit. Acceptable methods of contraception for female partners include:

- vasectomy of male partner
- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring

- surgical method (bilateral tubal ligation or regulatory approved method of hysteroscopic bilateral tubal occlusion)
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide.

Male subjects with partners of nonchildbearing potential must use a male barrier method of contraception (i.e., male condom with spermicide).

Male subjects are required to refrain from donation of sperm from Check-in through the EOS visit.

Sexual Abstinence

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 study and the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the ICF through the EOS visit.

Same-sex Relationships

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply.

If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception from the time of signing the ICF through EOS.

Appendix 4: Collection of Pregnancy and Lactation Information

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking study treatment through end of study (EOS).
- Information will be recorded on the Pregnancy Notification Form (see [Figure 3](#)). The form must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of learning 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(s), and/or noninvestigational product(s)/auxiliary medicinal product(s) through EOS. 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 report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse events 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 the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (e.g., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly), the Investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator will be reported to Amgen Global Patient Safety as described in [Appendix 1](#). 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 (see [Section 4.5](#) for details).

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

- In the event a male subject fathers a child during treatment through EOS, the information will be recorded on the Pregnancy Notification Form. The form (see [Figure 3](#)) must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking study treatment through EOS.
- Information will be recorded on the Lactation Notification Form ([Figure 4](#)) and submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the Investigator's knowledge of event.
- Study treatment will be discontinued if the female subject breastfeeds during the study.

With the female subject's 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 study treatment through EOS.

Figure 3: Pregnancy Notification Form

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: **PPD**

1. Case Administrative Information

Protocol/Study Number: AMGEN Protocol # 20220015 Supplier Protocol # 8524870

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

Confidential Medical and Scientific Affairs

Figure 4: Lactation Notification Form

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: PPD

1. Case Administrative Information

Protocol/Study Number: AMGEN Protocol # 20220015 Supplier Protocol # 8524870

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

Confidential Medical and Scientific Affairs

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) or Ethics Committee (EC) by the Investigator and reviewed and approved by the IRB or EC before the study is initiated.

UK site: Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

US sites: Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB or EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB or EC.
- Notifying the IRB or EC of serious adverse events or other significant safety findings as required by IRB or EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB or EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

An initial sample ICF will be provided for the Investigator (or designee) to prepare the informed consent document to be used at his or her site. Updates to the sample ICF are to be communicated formally in writing from the Study Manager to the Investigator. The written ICF is to be prepared in the language(s) of the potential study participant population.

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

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

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 ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records.

Subjects must be re-consented to the most current version of the ICF during their participation in the study.

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

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

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 21 days from the previous ICF signature date and the same version of the ICF is in use at the time of rescreening.

Subject Data Protection

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

Subjects will be assigned a unique identifier by the Sponsor (or designee). 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 electronic Case Report Form (eCRF) demographics page, in addition to the unique subject identification number (Section 4.4), include the age at time of enrollment.

For serious adverse events reported to the Sponsor (or designee), subjects are to be identified by their unique subject identification number (Section 4.4) (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 the Sponsor (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with 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/EC 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.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential information of the Sponsor, Amgen Inc. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor. The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written permission from the Sponsor.

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

Subjects will be assigned a unique identifier by the Sponsor (or designee). 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 eCRF demographics page, in addition to the unique subject identification number (Section 4.4), 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 (Section 4.4), 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 (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB or EC review, and regulatory agency inspections and provide direct access to source data documents.
- Fortrea is responsible for the data management of this study including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) (US sites) or in the study site archive for at least 5 years after the end of the study (UK site) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture system on an eCRF in a timely fashion.

All data generated from external sources (e.g., laboratory and bioanalytical data), and transmitted to Fortrea electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or Contract Research Organization,

will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the electronic data capture system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

The policy for publication of data obtained during this study will be documented in the Clinical Study Agreement.

Appendix 6: Hepatotoxicity: Suggested Actions and Follow-up Assessments

Subjects with normal hepatic function at Screening who experience aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations $> 3 \times$ upper limit of normal (ULN) or subjects with elevated values before drug exposure who have a 2-fold increase above baseline values (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009) are to undergo clinical assessments and a period of “close observation” until abnormalities return to normal or to the subject’s baseline level as described below.

Clinical Assessments and Observation

Assessments that are to be performed during this period include:

- Repeat AST, ALT, alkaline phosphatase, bilirubin (total and direct), and international normalized ratio (INR) within 24 hours, as possible
- In cases of total bilirubin (TBL) $> 2 \times$ ULN or INR > 1.5 , retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours, as possible, until laboratory abnormalities improve.

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize.

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

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G, 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 nonprescription 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 pharmacokinetic analysis 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 are 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 noninvestigational product(s)/auxiliary medicinal product(s).

The potential drug-induced liver injury (DILI) event and additional information such as medical history, concomitant medications, and laboratory results must be captured in the corresponding electronic Case Report Form (eCRF).

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

- Hepatobiliary tract disease
- Viral hepatitis (e.g., 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 (e.g., Gilbert’s syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (e.g., indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson’s disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (e.g., rhabdomyolysis, hemolysis).

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, i.e., cases of AST or ALT > 3 x ULN and concurrent TBL > 2 x ULN or INR > 1.5 (for subjects not on anticoagulation therapy) without evidence of alternative cause of the elevations, require the following:

- The event is to be reported to the Sponsor as a serious adverse event within 24 hours of discovery or notification of the event (i.e., before additional etiologic investigations have been concluded)
- The appropriate eCRF captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Sponsor.

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 [Appendix 1](#).

Appendix 7: Schedule of Assessments

[illegible]

Activity Per Period	Screening	Check-in	Treatment Period																						EOS/ET
Study Day	D-28 to D-2	-1 ^a	1	2	3	4	5	6	7	8	9	10	12	14	21	28	35	42	49	56	70	84	98	105	112
Time (Hours)			0	24	48	72	96	120	144	168	192	216	264	312	480	648	816	984	1152	1320	1656	1992	2328	2496	2664
PHARMACOKINETIC ASSESSMENTS																									
Rocatinlimab Serum PK ^k			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^d
CCI [REDACTED]			X ^l													X				X					X ^d
INVESTIGATIONAL PRODUCT																									
Rocatinlimab Dose Administration ^m			X																						

Abbreviations: BMI = body mass index; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; ET = early termination;

FSH = follicle-stimulating hormone; PK = pharmacokinetic.

^a Check-in activities to occur before Day 1.

^b In-house residency from Check-in through Day 14.

^c Interim medical history only.

^d Assessment to be performed at EOS or ET.

^e Adverse events will be recorded from initiation of study treatment on Day 1 until EOS completion. Adverse device events will be recorded from initiation of study treatment on Day 1 until EOS completion. Serious adverse events will be recorded from the time the subject signs the Informed Consent Form through 30 days after the last dose of study treatment or the EOS (whichever is later).

^f Prior and concomitant medication administration will be recorded beginning at informed consent. In addition, all Investigator-approved medications taken by a subject within 30 days or 5 half-lives (whichever is longer) before Check-in for over-the-counter or prescription medications, and 30 days prior to Check-in for herbal medicines (e.g., St. John's wort), vitamins, and supplements, will be recorded on the subject's electronic Case Report Form.

^g Performed in serum at Screening and in urine at all other times for all female subjects. A positive urine pregnancy test will be confirmed with a serum pregnancy test and may be further assessed with a quantitative beta human chorionic gonadotropin. Serum FSH test to be performed in all female subjects.

^h To be performed predose. On Day 1, vital signs will be performed predose and 30 minutes and 2 hours postdose. Supine blood pressure, supine pulse rate, respiratory rate, and oral body temperature. Heart rate and blood pressure will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes.

ⁱ Clinical chemistry (fasted at least 8 hours) and hematology.

^j eGFR will be calculated using the Modified Renal Disease equation. eGFR may be repeated at Check-in, if needed.

^k Rocatinlimab serum PK samples will be collected predose and postdose on Day 1. The predose PK sample will be collected within 30 minutes prior to dosing. The postdose PK samples will be collected 3 hours postdose, with a ± 15 -minute sampling window. Postdose samples collected on Days 2 to 14 will have a sampling window of ± 2 hours and postdose samples collected on Days 21 through 112 will have a sampling window of ± 48 hours. Times of all PK samples will be recorded to the nearest minute.

^l To be performed predose.

^m Dose administration of rocatinlimab is to occur during the morning of Day 1.

Approval Signatures

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Document Description: A Phase 1 Open-label, Randomized, Parallel-group Study to Assess the Relative Bioavailability of Rocatinlimab (AMG 451) Vial and Prefilled Syringe in Healthy Subjects

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