Protocol

A Phase I, Open-label, Randomized, Parallel-arm, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 133 Administered Subcutaneously in Healthy Japanese and Caucasian Subjects

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

NCT Number: NCT05056246
This NCT number has been applied to the document
for purposes of posting on Clinicaltrials.gov

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INVESTIGATOR AGREEMENT

I have read the protocol entitled "A Phase I, Open-label, Randomized, Parallel-arm, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 133 Administered Subcutaneously in Healthy Japanese and Caucasian 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 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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SYNOPSIS

Title of study: A Phase I, Open-label, Randomized, Parallel-arm, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 133 Administered Subcutaneously in Healthy Japanese and Caucasian Subjects

Objectives:

The primary objective of the study is:

- to evaluate the pharmacokinetics (PK) of AMG 133 after single subcutaneous (SC) administration in healthy Japanese and Caucasian subjects.

The secondary objectives of the study are:

- to evaluate the safety and tolerability of AMG 133 after single SC administration in healthy Japanese and Caucasian subjects.
- to evaluate the incidence of anti-AMG 133 antibodies in healthy Japanese and Caucasian subjects.

Study design:

This will be a Phase I, single-center, open-label, randomized, parallel-arm study to investigate the PK, safety, and tolerability of a single SC dose of AMG 133 in 3 groups of healthy Japanese subjects and 2 groups of healthy Caucasian subjects. Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to dose administration. Eligible subjects will be admitted into the clinical research unit (CRU) for Check-in on Day -1 and be confined to the CRU until clinic discharge on Day 8. On Day 1, 21 Japanese subjects will be randomly assigned in a 1:1:1 ratio to Group 1, 2, or 3, and 14 Caucasian subjects will be randomly assigned in a 1:1 ratio to either Group 4 or 5. Each subject will participate in 1 treatment group only.

Number of subjects:

Approximately 35 subjects will be enrolled in total, with 7 subjects in each of the 5 groups.

Diagnosis and main criteria for inclusion:

Healthy Japanese and Caucasian male or female subjects, 18 to 65 years of age (inclusive), and body mass index of 18 to 30 kg/m^2.

Investigational products, dose, and mode of administration:

Investigational Medicinal Product: [redacted] mg/mL solution AMG 133 administered via subcutaneous injection.

On Day 1, AMG 133 will be administered as a SC dose to the following groups:

- Group 1: [redacted] mg (Japanese subjects)
- Group 2: [redacted] mg (Japanese subjects)
- Group 3: [redacted] mg (Japanese subjects)
- Group 4: [redacted] mg (Caucasian subjects)
- Group 5: [redacted] mg (Caucasian subjects)

Duration of subject participation in the study:

Planned Screening duration: approximately 4 weeks.

Planned study duration (Screening to End of Study visit): approximately 21 weeks.

Primary endpoints:
The primary endpoints for this study are AMG 133 PK parameters: maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last}), and area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}).

Secondary endpoints:
Secondary endpoints for this study are: adverse events, clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, and incidence of anti-AMG 133 antibody formation.

Statistical methods:
The primary PK parameters will include C_{max}, AUC_{last}, and AUC_{inf} for AMG 133. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis.

The incidence and percentage of subjects who develop anti-AMG 133 antibodies (binding and if positive, neutralizing, when available) at any time will be tabulated by treatment group.

Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, 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.

Additional details will be included in the Statistical Analysis Plan.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	antidrug antibodies
ALT	alanine aminotransferase
AST	asparatate aminotransferase
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AV	atrioventricular
cAMP	cyclic adenosine monophosphate
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma concentration
CRU	clinical research unit
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EOS	end of study
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GLP-1	glucagon-like peptide 1
GLP-1R	GLP-1 receptor
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
INR	International normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IV	intravenous

mAb	monoclonal antibody
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's method
SC	subcutaneous
TBL	total bilirubin
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

Obesity (defined as body mass index of ≥ 30 kg/m^2)[2] is a major risk factor for type 2 diabetes mellitus and cardiovascular disease. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are gut-derived incretin hormones, known for their ability to augment glucose-stimulated insulin secretion through the GIP receptor (GIPR) and GLP-1 receptor (GLP-1R), respectively. In addition, GLP-1 is also known to promote satiety[3], while GIP has been shown to promote adiposity.[4,5]

1.1.1. Investigational Drug Product: AMG 133

AMG 133 is engineered by conjugation of a human monoclonal antihuman GIPR antagonist antibody (mAb) with 2 identical GLP-1 analog peptides, and therefore, exhibits both GIPR antagonism and GLP-1R agonism activities.

1.1.2. Pharmacology

In human embryonic kidney 293T cells stably expressing human GIPR, AMG 133 binds with a dissociation constant (Kd) of 37 pM and inhibits GIP-induced accumulation of cyclic adenosine monophosphate (cAMP), with a half-maximal inhibitory concentration (IC_{50}) of 42.4 nM. In addition, using a GLP-1 radioligand competition binding assay, AMG 133 binds to human GLP-1R with an IC_{50} of 55.2 nM. In Chinese hamster ovary K1 cells stably expressing human GLP-1R, AMG 133 binds to the GLP-1R and activates GLP-1 increasing cAMP levels with half-maximal effective concentration (EC50) of 24.4 pM.

In preclinical studies in obese cynomolgus monkeys, AMG 133 administration resulted in an approximate weight reduction of 17%, compared with vehicle, with concomitant decreases in food intake, insulin, and triglyceride levels.

1.2. Nonclinical Pharmacokinetics

AMG 133 pharmacokinetics (PK) is defined based on intact AMG 133 molecule (anti-GIPR mAb with at least 1 GLP-1 analog peptide) or total AMG 133 (anti-GIPR mAb with or without GLP-1 analog peptide).

The PK of AMG 133 has been evaluated in single-dose studies in the mouse and cynomolgus monkeys with a dose of 5 mg/kg intravenous (IV) and 3 mg/kg subcutaneous (SC), respectively. Exposure of intact and total AMG 133 were also evaluated in the mouse and cynomolgus monkey in repeat-dose toxicology studies including a 4-week exploratory study and a pivotal

Good Laboratory Practices-compliant 13-week SC repeat-dose. The doses evaluated in the 13-week GLP toxicology studies in mice ranged from 25 to 150 mg/kg and in cynomolgus monkeys from 20 to 120 mg/kg. In both the total and intact forms, AMG 133 exhibited linear pharmacokinetics in both mice and cynomolgus monkeys, regardless of the regimens (single or repeat) at all dose levels evaluated. Terminal half-life estimates in the obese cynomolgus monkeys ranged from 231 to 284 hours for total AMG 133, and from 189 to 222 hours for intact AMG 133. Some loss of the GLP-1 moiety of AMG 133 was observed in repeat-dose GLP mouse and cynomolgus monkey toxicology studies, but significant exposure of intact AMG 133 was maintained throughout the study.[1]

1.3. Nonclinical Toxicology

The cynomolgus monkey and the mouse were selected as the nonclinical toxicology species. In in vitro studies, AMG 133 binds with similar affinity to human, cynomolgus monkey, and mouse GIPR. Whereas AMG 133 functionally inhibits GIP signaling through human and cynomolgus monkey GIPR in vitro with equivalent potency, it has more than 20-fold lower potency for inhibition of GIP signaling through mouse GIPR. AMG 133 shows equivalent potency for human, cynomolgus monkey, and mouse GLP-1R. Despite the lower potency of AMG 133 for mouse GIPR, the high exposures obtained in the repeat-dose toxicology studies in the mouse likely achieved at least partial GIPR antagonism.

The studies conducted in the safety assessment of AMG 133 included exploratory 4-week SC repeat-dose and Good Laboratory Practice-compliant 13-week SC repeat-dose toxicology studies conducted in the mouse and the cynomolgus monkey. AMG 133-associated changes were limited to the anticipated pharmacological action of the molecule (eg, decreases in body weight, decreases in food consumption, atrophy of adipose tissue, decreased serum triglyceride in ≥ 1 studies) and minimal to moderate changes in red blood cell parameters and/or some clinical chemistry parameters, which are clinically monitorable. The no-observed-adverse-effect level for the 13-week SC repeat-dose toxicology studies in the mouse and the cynomolgus monkey was the highest tested doses of 150 and 120 mg/kg, respectively.

1.4. Preliminary Clinical Data

As of July 2021, a total of 49 subjects received a single dose of AMG 133 or placebo across doses ranging from 21 to 840 mg administered SC in the ongoing first-in-human (FIH) single-ascending-dose trial and eight subjects have received repeat-doses of AMG 133 [redacted] mg administered every 4 weeks or placebo in the ongoing multiple-dose trial. So far, AMG 133 (in SAD and MAD cohorts) has been generally well tolerated across the doses evaluated. No serious adverse events or deaths have been reported, and most adverse events reported were mild consisting of nausea, vomiting, and dyspepsia.

1.5. Study Rationale

AMG 133 has not been previously studied in healthy Japanese or healthy Caucasian subjects without obesity. The objective of this study is to evaluate the PK, safety, and tolerability of a

single SC dose of AMG 133 at 3 dose levels ([redacted], and [redacted] mg) in Japanese subjects and at 2 dose levels ([redacted] and [redacted] mg) in Caucasian subjects. This study will inform about any possible ethnic differences in PK between Japanese and Caucasian subjects.

1.6. Benefit-risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study. Refer to the IB[1] for more information.

1.6.1. Therapeutic Context

1.6.1.1. 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.

1.6.1.2. Key Potential Risks

To limit the risk of excessive exposure to healthy subjects in the current study, subjects will be administered as a single SC dose of AMG 133 at 3 dose levels ([redacted], and [redacted] mg) in Japanese subjects and at 2 dose levels ([redacted] and [redacted] mg) in Caucasian subjects (details provided in Section 3.3).

1.6.1.2.1. Gastrointestinal Tolerability Issues

Gastrointestinal tolerability issues including nausea, vomiting, and diarrhea are common adverse reactions for molecules targeting the obesity pathways. Gastrointestinal tolerability issues in humans are expected based on experience with marketed GLP-1R agonists. Subjects will be monitored for signs and symptoms of adverse events of nausea, vomiting, and diarrhea throughout the study.

1.6.1.2.2. Hypersensitivity Reactions

As with any biologic, administration of AMG 133 may result in systemic reactions including immune-mediated hypersensitivity. Drug hypersensitivity reactions typically occur during or within several hours after drug administration, but they may be delayed. Severe reactions may occur, including anaphylaxis, angioedema, and serum-like sickness. Potential anaphylactic reactions will be assessed by Sampson criteria. If Sampson criteria are positive, the potential anaphylactic reaction will be confirmed by measuring tryptase in blood plasma within 30 minutes of symptoms, and at any other time points as warranted and if feasible. AMG 133 will be administered by SC injection by a qualified clinical research staff member. Subjects will be monitored for signs and symptoms of hypersensitivity reactions during and after AMG 133 administration, such as fever, chills, shaking, hypotension, wheezing, itching, nausea, and/or rash.

1.6.1.2.3. Injection Site Reactions

Injection site reactions (eg, erythema, itching, hematoma, swelling, bruising, and pain) are common side effects of drugs with SC administration. These reactions can range from mild to severe (including injection site necrosis, which is an uncommon side effect). After SC administration, subjects will be monitored for injection site reactions, which may include redness, tenderness/pain, bruising, warmth, swelling, itching, and/or infection. If appropriate, photographic documentation of injection site reactions will be obtained.

1.6.1.2.4. Immunogenicity

As with all biological products, there is a potential for the development of anti-AMG 133 antibodies. The potential effects of anti-AMG 133 antibodies on subjects who might develop them are not known, but reduced efficacy of AMG 133 is a possibility. Subjects will be monitored for potential effects of antidrug antibodies (ADA) that may include antibody-mediated adverse events, altered drug exposure, or loss of efficacy. Pharmacokinetic and immunogenicity samples from subjects in this Phase I study will be collected from study subjects at protocol-defined intervals and analyzed to monitor the development of anti-AMG 133 antibodies. Positive samples will be titrated and evaluated for neutralizing antibodies. Additional blood samples may be obtained to evaluate any ADA-mediated effects on safety during the study.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the IB for further data on potential side effects of AMG 133.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to evaluate the PK of AMG 133 after single SC administration in healthy Japanese and Caucasian subjects.

The secondary objectives of the study are:

- to evaluate the safety and tolerability of AMG 133 after single SC administration in healthy Japanese and Caucasian subjects.
- to evaluate the incidence of anti-AMG 133 antibodies in healthy Japanese and Caucasian subjects.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

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

2.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- adverse events
- clinical laboratory tests
- 12-lead electrocardiograms (ECGs)
- vital signs
- incidence of anti-AMG 133 antibodies.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This will be a Phase I, single-center, open-label, randomized, parallel-arm study to investigate the PK, safety, and tolerability of a single SC dose of AMG 133 in 3 groups of healthy Japanese subjects and 2 groups of healthy Caucasian subjects.

Approximately 35 subjects will be enrolled in total, with 7 subjects in each of the 5 groups.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to dose administration. Eligible subjects will be admitted into the clinical research unit (CRU) for Check-in on Day -1 and be confined to the CRU until clinic discharge on Day 8. On Day 1, 21 Japanese subjects will be randomly assigned in a 1:1:1 ratio to Group 1, 2, or 3, and 14 Caucasian subjects will be randomly assigned in a 1:1 ratio to either Group 4 or 5. Each subject will participate in 1 treatment group only.

On Day 1, AMG 133 will be administered as a single SC dose to the following groups:

- Group 1: [redacted] mg (Japanese subjects)

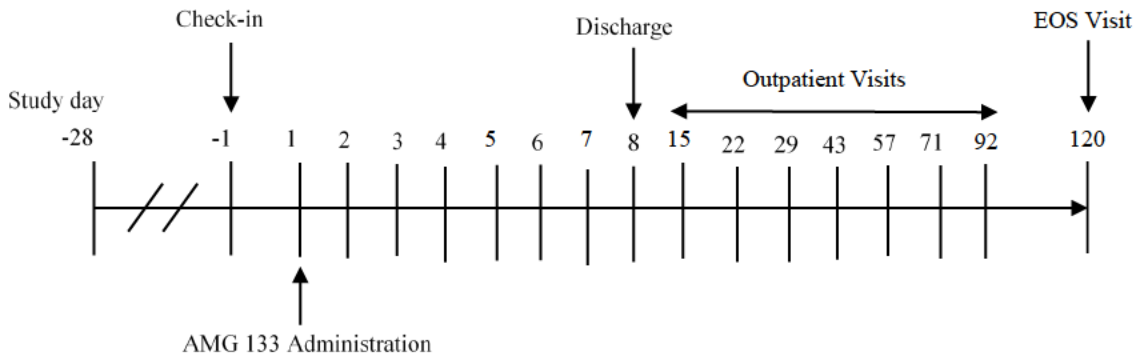
- Group 2: [redacted] mg (Japanese subjects)
- Group 3: [redacted] mg (Japanese subjects)
- Group 4: [redacted] mg (Caucasian subjects)
- Group 5: [redacted] mg (Caucasian subjects)

The total duration of study participation for each subject (from Screening through end of study [EOS] visit) is anticipated to be approximately 21 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).

An overview of the study design is shown in Figure 1. A Schedule of Assessments is presented in Appendix 8.

Figure 1: Study Design



3.2. Discussion of Study Design

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 concomitant medications.

3.3. Selection of Doses in the Study

The selection of the doses being evaluated in this study is based on the preliminary PK, safety, and tolerability data from an ongoing FIH study (20180048) evaluating AMG 133 in adult subjects with obesity at single doses ranging from 21 to 840 mg, and multiple-ascending doses following [redacted] mg administered every 4 weeks (total of 3 doses). In general, AMG 133 has been shown to be safe and well tolerated across the studied dose ranges (21 to 840 mg). The

preliminary PK data from this study demonstrate that intact AMG 133 and total AMG 133 plasma exposures increase in a dose-proportional manner.

The doses [redacted], and [redacted] mg are selected for evaluation in Japanese subjects and will enable an assessment of pharmacokinetic linearity within the AMG 133 dose range that is anticipated to be clinically relevant. The highest dose of [redacted] mg is selected as this is the highest dose planned for the ongoing multiple-ascending-dose study [redacted] mg administered every 4 weeks) and is the highest anticipated dose to be tested in a Phase 2 study.

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. Japanese subjects must be first-generation Japanese (4 grandparents, biological parents, and subject born in Japan).
3. Healthy male or female subjects between 18 and 65 years of age (inclusive) at the time of Screening.
4. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) as assessed by the Investigator (or designee).
5. Body mass index between 18 and 30 kg/m^2 at the time of Screening.
6. Females of nonchildbearing potential defined as permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) or postmenopausal (defined as at least 45 years of age with amenorrhea for 12 months without an alternative medical cause and follicle-stimulating hormone [FSH] level $\geq$ 40 mIU/mL).

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:

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 current signs or symptoms of cardiovascular disease, including, but not limited to, myocardial infarction, congenital heart disease, valvular heart disease, coronary revascularization, or angina.
3. History or evidence of clinically significant arrhythmia at Screening, including any clinically significant findings on the ECG taken at Check-in.
4. A QT interval corrected for heart rate (HR) based on the Fridericia method (QTcF) interval >450 ms in male subjects or >470 msec in female subjects or history/evidence of long QT syndrome (confirmed by calculating the mean of the original value and 2 repeats) at Screening or Check-in.
5. PR interval >200 ms, second-degree atrioventricular (AV) block, or third-degree AV block at Screening or Check-in.
6. Systolic blood pressure >140 mmHg or < 90 mmHg, or diastolic blood pressure >90 mmHg, or HR >100 bpm at Screening or Check-in.
7. History of hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee) and in consultation with the Sponsor.
8. Poor peripheral venous access.
9. Estimated glomerular filtration rate less than ≤ 80 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation at Screening or Check-in.
10. Alanine aminotransferase or aspartate aminotransferase > the upper limit of normal at Screening or Check-in.
11. Positive hepatitis B or hepatitis C panel and/or positive human immunodeficiency virus test at Screening. Subjects whose results are compatible with prior immunity (vaccination or prior infection) may be included.
12. Use of any over-the-counter or prescription medications within 30 days or 5 half-lives (whichever is longer) before Check-in.
    a. Acetaminophen (paracetamol; up to 2 g per day) for analgesia will be allowed.
    b. Hormone replacement therapy (eg, estrogen) will be allowed.
13. All herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within the 30 days prior to enrollment, unless deemed acceptable by the Investigator (or designee) and in consultation with the Sponsor.
14. Consumption of foods and beverages containing poppy seeds within 7 days prior to Check-in.
15. History of alcoholism or drug/chemical abuse within 1 year prior to Check-in.

16. Alcohol consumption from 48 hours prior to Check-in and prior to each clinic visit and agrees to limit alcohol intake to a maximum of 1 unit/day on all other days, while not in the CRU, from Screening through the EOS visit.
17. Regular alcohol consumption of >14 units per week for males and >7 units for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
18. Use of tobacco- or nicotine-containing products within 6 months prior to Check-in.
19. Unwilling to maintain normal level of physical activity from 7 days before Check-in until the EOS visit (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).
20. Positive test for illicit drugs, cotinine (tobacco or nicotine use), and/or alcohol use at Screening or Check-in.
21. Consumption of caffeine-containing foods and beverages within 48 hours prior to Check-in.
22. Female subjects with a positive pregnancy test at Screening or Check-in.
23. Female subjects lactating/breastfeeding or who plans to breastfeed during the study through 90 days after the EOS visit.
24. Unwilling to adhere to contraceptive requirements through 90 days after the EOS visit (see Appendix 4).
25. Unwilling to abstain from sperm donation through 90 days after the EOS visit (see Appendix 4).
26. Male subjects with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
27. Male subjects with a pregnant partner or partner planning to become pregnant who are unwilling to practice abstinence (refrain from heterosexual intercourse) or use contraception while the subject is on study through 90 days after the EOS visit.
28. 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.
29. Have previously completed or withdrawn from this study or any other study investigating AMG 133 or have previously received the investigational product.
30. Donation of blood from 3 months prior to Check-in, plasma from 2 weeks prior to Check-in, or platelets from 6 weeks prior to Check-in.
31. Unwilling to abide with study restrictions.
32. 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 will be collected that includes 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. Subject Number and Identification

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects 0101, 0102, 0103). Replacement subjects will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

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 8). 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 clinic. The Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their adverse events, serious adverse events, or until the unresolved adverse events, 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) 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 investigational product 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 IMP and non-IMP, respectively.

5.1. Investigational Product

The IMP will be supplied by the Sponsor. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of the IMP shown in Table 1.

All supplies of investigational product, both bulk and subject-specific, will be stored in accordance with the manufacturer’s instructions or pharmacy instructions. Until dispensed to the subjects, the investigational and non-investigational products will be stored at the study site in a location that is locked with restricted access.

For preparation instructions, refer to the IPIM.

Table 1: Investigational Product

Study Treatment Name	Investigational Medicinal Product: AMG 133
Unit Strength and Formulation	[redacted] mg/mL solution
Dosage Level	[redacted]
Route of Administration	Subcutaneous Injection
Diet Requirements	Fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations
Diet Restrictions	Foods and beverages containing poppy seeds will not be allowed from 7 days prior to enrollment until EOS visit Caffeine-containing foods and beverages will not be allowed from 48 hours before each study visit through the EOS visit Consumption of alcohol will not be permitted from 48 hours prior to each clinic visit, 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.
Dosing Instructions	Administration of AMG 133 or requires specific training, which must be completed and documented before undertaking any administration related activities. AMG 133 will be delivered as [redacted] injections SC. AMG 133 should be administered in the abdomen by SC injection. Where [redacted] injection is required to administer the full dose, the subject will receive the SC injections in different quadrants in the abdomen in a consecutive fashion with the injections separated by no more than 1 minute. Each injection should be separated by a minimum of 2 inches. Each quadrant may be injected once with up to [redacted] mL of AMG 133 in the order described above. Additional dosing instructions are provided in the Investigational Product Instruction Manual (IPIM).

5.2. Investigational Product Administration

Each SC injection will be administered by qualified and appropriately trained clinical staff to different quadrants in the abdomen. There are no posture requirements for dosing (see Table 1). In the [redacted] mg dose group, [redacted] injection with a total volume of [redacted] mL will be administered. In the [redacted] and [redacted] mg dose groups, [redacted] injections and [redacted] injections, respectively, of [redacted] mL each will be administered. Where multiple injections are administered, the injection sites will be located in different quadrants of the abdomen.

5.3. Treatment of Overdose

The effects of overdose of AMG 133 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 overdose, and to discuss further management of the subject.

5.3.1. Medical Devices

No investigational medical device(s) will be used in this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care. Non-Amgen non-investigational medical devices (eg, syringes, sterile needles) that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The Investigator will be responsible for obtaining supplies of these devices.

5.3.2. 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(s) or device(s) after it is released for distribution to market or clinic by either the Sponsor or by distributors and partners for whom the Sponsor manufactures the material. This includes any investigational product (AMG 133) provisioned and/or repackaged/modified by the Sponsor.

Any product complaint(s) associated with an investigational product (AMG 133) supplied by the Sponsor are to be reported according to the instructions provided in the Amgen IPIM.

5.4. Randomization

This is a randomized, parallel-arm study. Japanese subjects will be randomized (1:1:1) to 1 of the 3 treatment groups, and Caucasian subjects will be randomized (1:1) to 1 of the 2 treatment groups. Randomization scheme will be provided by a biostatistician.

5.5. Blinding

This is an open-label study.

5.6. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of the Investigator or designee.
- At each dosing occasion, a predose and postdose inventory of AMG 133 will be performed.

5.7. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of AMG 133 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. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused AMG 133 will be returned to the Sponsor, retained at the study site, or disposed of by the study site, per the Sponsor's written instructions.

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) or hormone replacement therapy 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. While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Refer to Section 5 and Table 1 for diet requirements/restrictions on applicable days of study treatment and/or PK assessments.

Foods and beverages containing poppy seeds will not be allowed from 7 days prior to Check-in until EOS visit.

Caffeine-containing foods and beverages will not be allowed from 48 hours before each study visit through the EOS visit.

Consumption of alcohol will not be permitted from 48 hours prior to each clinic visit, 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 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 (ie, 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 3 months 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):

- dosing
- safety assessments (ECGs will be scheduled before vital signs measurements)
- PK blood samples
- antidrug antibody samples
- 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 clinical laboratory assessments.

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 8. 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 8) 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

Plasma concentrations of AMG 133 will be determined using validated analytical procedures. Specifics of the analytical method will be provided in a separate document (ie, Statistical Analysis Plan).

7.2. Antidrug Antibody Assessments

Serum samples for antibody testing are to be collected as outlined in the Schedule of Assessments in Appendix 8.

Bioanalytical testing for anti-AMG 133 antibodies will be conducted on these samples using a fully validated, electrochemiluminescence-based immunoassay. All samples that test positive for ADA will be titered and evaluated for neutralizing antibodies against human GLP-1 using a cell-based assay. All neutralizing antibody positive subjects and subjects who tested positive for binding ADAs at the final scheduled study visit, defined as the EOS visit, and have clinical sequelae that are considered potentially related to an anti-AMG 133 antibody response will be asked to return for additional follow-up testing until the ADA responses have returned to (1) baseline, (2) a low titer, or (3) the subject has been followed for a period of at least 1 year (±4 weeks) post-administration of AMG 133. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive AMG 133.

7.3. Safety and Tolerability Assessments

7.3.1. Adverse Events 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 and serious adverse events are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to EOS visit. 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 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 enrollment through the EOS visit are recorded/reported using the appropriate eCRF.

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 within 24 hours of the Investigator's knowledge of the event. The Investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events should be reported to Amgen (regardless of causality) if the Investigator becomes aware of them. Per local requirements in some countries, Investigators are required to report serious adverse events that they become aware of after EOS. If serious adverse events are reported, the Investigator is to report them to the Sponsor within 24 hours following the Investigator's knowledge/awareness of the event using the paper-based Serious Adverse Event Report Form.

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 investigational product.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to 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 within 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 subject is permanently withdrawn from protocol-required therapies 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/IECs, and Investigators.

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

An Investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the

Sponsor will file it along with the IB and will notify the IRB, if appropriate according to local requirements.

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.

If a pregnancy is reported, the Investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow up with the Investigator regarding additional information that may be requested.

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

Further details regarding pregnancy and lactation are provided in Appendix 5.

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 8. 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 CRF/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 judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath or urine test at the times indicated in the Schedule of Assessments in Appendix 8. For all female subjects, a pregnancy test and FSH screen for postmenopausal women will be performed at the times indicated in the Schedule of Assessments in Appendix 8.

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

7.3.3. Vital Signs

Supine blood pressure, supine heart rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 8. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

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 heart 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 8. 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 or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.3.5. Physical Examination

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in Appendix 8.

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

The sample size for this study is based practical considerations. No statistical hypotheses will be tested. Approximately 35 subjects will be enrolled across 5 groups (7 subjects per group). The study design and sample size per dose group for this study is considered adequate for evaluation of the study objectives.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of AMG 133 and have evaluable PK data.

8.2.2. Safety Population

The safety population will include all subjects who received at least 1 dose of AMG 133.

8.3. Pharmacokinetic Analyses

Plasma AMG 133 concentrations will be determined using a validated assay. Individual plasma concentration-time plots for AMG 133 will be presented for each subject as well as mean concentration-time plots for each dose group. Pharmacokinetics parameters of AMG 133 will be calculated using standard noncompartmental methods.

The primary PK parameters will include C_{max}, AUC_{last}, and AUC_{inf} for AMG 133. All other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis.

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

8.4. Antidrug Antibody Analysis

The incidence and percentage of subjects who develop anti-AMG 133 antibodies (binding and if positive, neutralizing, when available) at any time will be tabulated by treatment group.

8.5. 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 or other protocol-required therapies, 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.

8.6. Interim Analysis

No interim analyses are planned for this study.

9. REFERENCES

1. Amgen Inc. AMG 133 – Investigator's Brochure (Version 1.0). 01 June 2020.

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4. Yip RG, Boylan MO, Kieffer TJ, Wolfe MM. Functional GIP receptors are present on adipocytes. Endocrinology. 1998;139:4004-4007

5. Beck B, Max JP. Hypersensitivity of adipose tissue to gastric inhibitory polypeptide action in the obese Zucker rat. Cell Mol Biol. 1987;33:555-562.

10. APPENDICES

Appendix 1: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events, 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 (ie, 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of 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. For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or

hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

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

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant adverse event/serious adverse event information in the 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, other protocol-required therapies;
  - 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 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 Amgen grading scale:

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), protocol-required therapy, and/or study-mandated procedure 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 protocol-required therapies because of a serious adverse event, this information must be submitted to the Sponsor.
- If a subject dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- 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) should be reported to Amgen (regardless of causality) 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.

Figure 2: Sample Serious Adverse Event Report Form

AMGEN 20200290 LabCorp. Study # 8473020 AMG 133	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

Amgen (Sponsor) US Safety Fax Number: + 1 (888) 814-8653
If FAX is unavailable, email form to the following address: svc-ags-in-us@amgen.com

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 *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.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria 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? If yes see section 10 AMG133 <<Device>> <<Device>> <<Device>> <<Device>> No Yes	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **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

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ❑No ❑Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 133 ❑Blinded X Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial #_____ ❑ Unknown
<<IP/Device>> ❑Blinded ❑Open Label							Lot #_____ ❑ Unknown Serial:_____ ❑ Unknown

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AMGEN 20200290 LabCorp. Study # 8473020 AMG 133	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

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AMGEN 20200290 LabCorp. Study # 8473020 AMG 133	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	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 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.*		

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Amylase Lipase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Creatinine Kinase Hemoglobin A1C High-density lipoprotein (HDL) Low-density lipoprotein (LDL) Lactate dehydrogenase (LDH) Direct bilirubin[a] Gamma-glutamyl transferase Glucose Indirect bilirubin[a] Inorganic phosphate Magnesium Phosphorus Potassium Sodium Total bilirubin[a] Total creatine kinase 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 Reticulocytes White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Segmented Neutrophils Bands/Stabs	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[c]:**	**Hormone panel - females only:**
Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/ cannabinoids Tricyclic antidepressants Cotinine test Alcohol breath or urine test	Follicle-stimulating hormone (postmenopausal females only) [b] Serum pregnancy test (human chorionic gonadotropin)[d] Urine pregnancy test[d]
		Other tests:
		Hepatotoxicity only: International normalized ratio (INR)[e] Estimated glomerular filtration rate (eGFR)[f]

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Only analyzed at Screening.

[c] Only analyzed at Screening and Check-in. Alcohol testing is not included at Screening. Cotinine testing at Screening, Check-in, and all outpatient visits.
[d] 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.
[e] International normalized ratio will be tested if hepatotoxicity is suspected, per guidelines presented in Appendix 7.
[f] Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease equation.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical laboratory evaluations	7.5	8	60
Serology	3.5	1	3.5
Serum FSH	4	1	4
Serum pregnancy test	4	1	4
AMG 133 pharmacokinetics	4	16	64
Anti-AMG 133 antibody	4	5	20
Total:			155.5

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: 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 and for 90 days after 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.

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

Women of Nonchildbearing Potential:

1. **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.
2. **Postmenopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone 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.

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

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Requirements

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception.

Male Subjects:

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception by female partner from Check-in until 90 days after the EOS visit. Acceptable methods of contraception for female partners include:

- 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 are required to refrain from donation of sperm from Check-in until 90 days after the EOS visit.

Sexual Abstinence

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, 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 until 90 days after the EOS visit.

Same-sex Relationships

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

A subject in a same-sex relationship at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 90 days after the EOS visit.

Appendix 5: 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 protocol-required therapies through 90 days after EOS.
- Information will be recorded on the Pregnancy Notification Form (see Figure 3: Pregnancy Notification Form). The form must be submitted to Amgen Global Patient Safety within 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 region's local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 90 days after 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 event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to the Sponsor as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, 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 5.6 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, and for an additional 90 days after EOS, the information will be recorded on the Pregnancy Notification Form. The

form (see Figure 3: Pregnancy Notification Form) must be submitted to Amgen Global Patient Safety within 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 region's local privacy laws).

- The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 90 days after EOS.
- Information will be recorded on the Lactation Notification Form (Figure 4) and submitted to Amgen Global Patient Safety within 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 protocol-required therapies through 90 days after discontinuing protocol-required therapies.

Figure 3: Pregnancy Notification Form

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20200290 LabCorp Study # 8473020

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
AMG 133				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

Figure 4: Lactation Notification Form

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20200290 LabCorp. Study # 8473020

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 133				mm____/dd____/yyyy____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Appendix 6: 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 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 (eg, advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious adverse events or other significant safety findings as required by IRB 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, 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 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 28 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 (eg, 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 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.

Subject 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 CRF 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 (eg, 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 (eg, 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 review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. 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), 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 (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or designee 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 EDC 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 7: 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 x 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
- In cases of total bilirubin (TBL) >2 x ULN or INR >1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve.

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

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 protocol-required therapies.

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

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, ie, 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 (ie, 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 8: Schedule of Assessments

Schedule of Assessments

Activity	Screening	Check-in	Treatment Period															EOS/ET[a]
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**92**	**120**
Relative to Dosing (hours)			Predose	24	48	72	96	120	144	168	336	504	672	1008	1344	1680	2184	2856
In-house Residency		◄	―	―	―	―	―	―	―	►								
Outpatient Visit	X									X	X	X	X	X	X	X	X	X
GENERAL AND SAFETY ASSESSMENTS																		
Informed Consent	X																	
Inclusion/Exclusion Criteria Eligibility Review	X	X																
Medical History	X	X[b]																
Height, Weight, and BMI	X	X[c]																
Drug Screen	X[d]	X																
Cotinine Test	X	X																
Adverse Events[e]			◄	―	―	―	―	―	―	―	―	―	―	―	―	―	―	►
Serious Adverse Events[e]	◄	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	►
Concomitant Medications[f]	◄	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	―	►
Pregnancy Test (females only)[g]	X	X																X
Serology	X																	
FSH Test[h]	X																	
12-lead ECG[i]	X	X	X															X
Vital Signs[j]	X	X	X	X	X					X	X	X	X	X	X	X	X	X
Clinical Chemistry, Urinalysis, and Hematology[k]	X	X			X					X			X		X		X	X
eGFR[l]	X	X																
Physical Examination[m]	X	X			X								X		X	X	X	X
PHARMACOKINETIC ASSESSMENTS																		
AMG 133 Plasma PK Samples[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-AMG 133 Antibody Serum Sample			X								X		X		X			X
INVESTIGATIONAL PRODUCT																		
AMG 133 Dose Administration[o]			X															

Abbreviations: BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; ET = early termination; FSH = follicle-stimulating hormone; PK = pharmacokinetic.

[a] All neutralizing antibody positive subjects and subjects who tested positive for binding ADAs at the final scheduled study visit, defined as the end of study visit, and have clinical sequelae that are considered potentially related to an anti-AMG 133 antibody response will be asked to return for additional follow-up testing until the ADA responses have returned to (1) baseline, (2) a low titer, or (3) the subject has been followed for a period of at least 1 year (± 4 weeks) post-administration of AMG 133.

[b] Interim medical history only.

[c] Weight and BMI only.

[d] Alcohol testing is not included at Screening.

[e] Adverse 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 until 30 days postdose or EOS visit, 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 enrollment for herbal medicines (eg, 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 females. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

[h] Performed in postmenopausal females only.

[i] Electrocardiograms will be collected after the subject has rested in a supine position for at least 5 minutes, and will be obtained prior to the scheduled blood draws.

[j] Supine blood pressure, supine heart rate, respiratory rate, and oral body temperature will be measured after the subject has been resting in the supine position for at least 5 minutes.

[k] Clinical chemistry fasted at least 8 hours.

[l] eGFR will be calculated using the Modified Renal Disease equation.

[m] A full physical examination at Screening and Check-in and a symptom-directed physical examination at other timepoints.

[n] The PK sample collected from predose through 48 hours postdose will have a sampling window of ± 30 minutes, samples collected at outpatient visits will have a sampling window of ± 48 hours. Times of all PK samples will be recorded to the nearest minute.

[o] Dose administration of AMG 133 is to occur during the morning of Day 1 after an overnight fast of at least 10 hours.

Summary of Amended Protocol Changes

A Phase I, Open-label, Randomized, Parallel-arm, Single-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 133 Administered Subcutaneously in Healthy Japanese and Caucasian Subjects

Protocol Status: Final
Original Protocol Date: 09 August 2021
Protocol Date: 24 August 2021

Investigational Drug: AMG 133

Amgen Protocol Reference Number: 20200290
Labcorp Drug Development Study: 8473020

Sponsor:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320, USA

Study Site:
Labcorp Drug Development
3402 Kinsman Boulevard
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[redacted]

Principal Investigator:
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The primary change in this amendment is:

1. to update the number of injections in the [redacted] mg dose group from [redacted]

Minor changes:

1. The version number and date were updated throughout the protocol.

2. Typographical errors and formatting errors were corrected, as necessary.

A detailed summary of changes is presented below:

5.2. Investigational Product Administration

Previously read:

Each SC injection will be administered by qualified and appropriately trained clinical staff to different quadrants in the abdomen. There are no posture requirements for dosing (see Table 1). In the [redacted] mg dose group [redacted] injection with a total volume of [redacted] mL will be administered. In the [redacted] and [redacted] mg dose groups [redacted] injections and [redacted] injections, respectively, of [redacted] mL each will be administered. Where multiple injections are administered the injection site in different quadrants of the abdomen.

Now reads:

Each SC injection will be administered by qualified and appropriately trained clinical staff to different quadrants in the abdomen. There are no posture requirements for dosing (see Table 1). In the [redacted] mg dose group, [redacted] injection with a total volume of [redacted] mL will be administered. In the [redacted] and [redacted] mg dose groups, [redacted] injections and [redacted] injections, respectively, of [redacted] mL each will be administered. Where multiple injections are administered, the injection sites will be located in different quadrants of the abdomen.