Title Page

Protocol Title:		A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 133 in Subjects With Obesity
Short Protocol Title:		Single and Multiple Ascending Dose Study of AMG 133 in Subjects with Obesity
Protocol Number:		20180048
Investigational Product:		AMG 133
Sponsor	**Name of Sponsor:**	Amgen Inc.
	Address:	One Amgen Center Drive, Thousand Oaks, CA, 91320, USA
	Telephone Number:	+1 (805) 447-1000
Protocol Approver	**Name:**	[redacted]
	Function:	Executive Medical Director, Translational Medicine
Key Sponsor Contact	**Name:**	[redacted] MD, PhD
	Address:	One Amgen Center Drive, Thousand Oaks, CA, 91320, USA
	Telephone Number:	[redacted]
	Email Address:	
NCT Number:		NCT04478708
Protocol Version Date:		**Document Version** / **Date** **Original** 13 May 2020 **Amendment 1 (v1.0)** 19 November 2020 **Amendment 2 (v2.0)** 08 February 2021 **Amendment 3 (v3.0)** 14 May 2021 **Amendment 4 (v4.0)** **03 February 2022**
Data Elements Standards Version:		6.4

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

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 133 in Subjects With Obesity, dated **03 February 2022**, and agree to abide by all provisions set forth therein.

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

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

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 133 in Subjects With Obesity

Short Protocol Title: Single and Multiple Ascending Dose Study of AMG 133 in Subjects with Obesity

Study Phase: 1

Indication: Obesity

Rationale

Obesity is a growing global health crisis that is in critical need of safe and effective therapies. Currently approved products provide modest weight loss with side effects that include gastrointestinal intolerability. AMG 133 is a peptide conjugated antibody composed of a human monoclonal antibody (mAb) that binds to and blocks the glucose dependent insulinotropic polypeptide receptor (GIPR) conjugated to 2 identical peptides. The conjugated peptides are glucagon-like peptide 1 receptor agonists. 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. The current study evaluates the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) of single ascending doses (SADs) and multiple ascending doses (MADs) of AMG 133 as a potential therapy for the treatment of obesity.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of AMG 133 as single and multiple doses in subjects with obesity	• Subject incidence of treatment-emergent adverse events. • Changes in laboratory safety tests, vital signs, and 12-lead electrocardiograms (ECGs)
Secondary	
• To characterize the pharmacokinetics of AMG 133 as single or multiple doses in subjects with obesity	• AMG 133 pharmacokinetic parameters including, but not limited to, maximum observed drug concentration during a dosing interval (C_{max}), the time of maximum observed concentration (t_{max}), and area under the concentration-time curve (AUC)
• To evaluate the immunogenicity of AMG 133	• Incidence of anti-AMG 133 antibody formation

Overall Design

Part A (cohorts 1 **to** 6 and cohort 11) is a phase 1, randomized, double-blind, placebo-controlled, SAD study in adult subjects with obesity. AMG 133 will be administered by subcutaneous (SC) injection for cohorts 1 to 5 and cohort 11, and intravenous (IV) injection for cohort 6. Part A consists of a total of 7 cohorts.

Subjects will be confined at the Clinical Research Unit from check-in (morning of day -2) through the morning of day 8 for cohorts 1 to 5 and cohort 11 and day 6 for cohort 6.

Approximately 56 subjects will enroll into 1 of 7 cohorts. In each cohort, 8 subjects will be randomized to receive AMG 133 or placebo SC (cohorts 1 to 5 and cohort 11) or IV (cohort 6) in a 3:1 ratio as described below. For cohort 1, the first 2 subjects (sentinel pair) will be randomized such that 1 subject will receive AMG 133 and 1 subject will receive placebo. The sentinel pair will be observed for at least 48 hours before the remaining subjects in the cohort are dosed, provided there are no safety or tolerability concerns as assessed by the investigator. Enrollment into the SAD cohorts will be sequential. Subsequent cohorts will be dosed after the dosing regimen in the preceding cohort has been recommended by the Dose Level Review Team (DLRT) to be safe and well tolerated based on the safety and laboratory data through at least day 15 for at least 7 out of 8 subjects dosed. Subjects in cohorts 1 to 5 and cohort 11 will also participate in [redacted] tests at day -1 and day 7.

Part B (cohorts 7 **to** 10) is a randomized, placebo-controlled, double-blind, MAD study in adult subjects with obesity. In each cohort, subjects will be randomized to receive AMG 133 or placebo SC in a 3:1 ratio as described in **Table 7**.

Approximately 24 subjects will enroll into cohorts 7 **to** 9 (8 subjects per cohort). Cohorts 7 **to** 9 will include assessments of [redacted]. Enrollment into Part B cohort 7 will occur with a starting MAD dose that is at least 2 SAD dose levels below what was recommended by the DLRT to be safe and reasonably tolerated in Part A. Enrollment into the MAD cohorts 8 and 9 will be sequential.

Subjects in cohorts 8 and 9 will be dosed after the dose regimen in the preceding MAD cohort has been recommended by the DLRT to be safe and reasonably tolerated based on safety and laboratory data through at least study day 36 for 6 out of 8 subjects dosed.

The DLRT for SAD cohort 11 will also make dosing recommendations for cohort 9 (Figure 1-1 [A]). [redacted]

Cohort 10 will enroll **up to** 20 subjects and will include the use of [redacted] Therefore, the dose recommended for cohort 10 should be the same as a dose studied in a previous **MAD** cohort.

The dose recommended for cohort 10 will depend on the final dose recommended for cohort 9 and the safety and tolerability profiles for MAD cohorts 7 and 8 (Figure 1-1 [B]).

[redacted]

[redacted]

In all dose escalation process **between cohorts**, DRLM will make a recommendation and Amgen will make the final decision on dose level.

Part C (cohort 12 to 13) is an open-label modified dose-escalation MAD study in subjects with obesity. Doses selected for these cohorts have been doses previously studied in Part A and Part B and have been shown to have an acceptable safety and tolerability profile. Doses selected in Part C will not exceed the dose levels previously studied in the MAD cohorts (420 mg SC Q4Wx 3). Cohort 12 will receive [redacted] mg SC on days [redacted] followed by [redacted] mg SC on days [redacted]. Cohort 13 will receive [redacted] mg SC on days [redacted] followed by [redacted] mg SC on days [redacted]. Up to 6 subjects per cohort will receive AMG 133 as described in Section 1.3. Cohort 12 and cohort 13 will enroll in parallel. The DLRT will review the safety and laboratory data through at least day 36.

Figure 1-1. Dose Selection for Cohort 9 and 10

- MAD cohorts 7 **to** 9: Study drug will be administered every 4 weeks for a total of 3 SC doses. The dose levels will be defined after evaluation of the available PK and PD data from preceding cohorts in the SAD phase (Part A). Three different dose levels will be evaluated with the lowest dose administered to cohort 7, and 2 higher ascending doses administered to cohorts 8 and 9. The dose level for cohorts 7 **to** 9 will not exceed the highest dose evaluated in cohorts 1 **to** 6 and cohort 11 (Part A). Subjects enrolled in cohorts 7 **to** 9 will also be asked to [redacted]
- MAD cohort 10: **Up to t**wenty subjects will be randomized in a 3:1 ratio to receive AMG 133 or placebo SC. All subjects will be asked to use [redacted]
  The dose level will be defined after evaluation of the available PK and PD data from preceding MAD cohorts. The dose level will not exceed the highest dose evaluated in cohorts 7 **to** 9 (Part B).

Dose Level Review Meetings

A DLRM will be held to review subject data and monitor safety before escalation to the next cohort. Escalation to a higher dose cohort will only proceed when the previous dose regimen and cumulative data from previous cohorts have been reviewed and found to be safe and reasonably tolerated based on available safety and laboratory data through day 15 for at least 7 out of 8 subjects dosed in Part A and day 36 for Part B for at least 6 out of 8 subjects dosed and upon unanimous agreement of the DLRT members.

The planned dose escalation schedule may be modified based on treatment-emergent data (safety and/or PD). Dose adjustments (if any) will be made by Amgen on a treatment cohort and not on an individual basis.

The doses selected for Part C cohorts are those that have already been shown to have an acceptable safety and tolerability profile. The DLRT will meet to review the safety and tolerability through at least day 36.

Number of Subjects

A total of approximately **112** subjects will be enrolled in the study. Approximately 56 subjects will be enrolled in Part A of the study, with 8 subjects in each of the 7 cohorts. Approximately 44 subjects will be enrolled in Part B of the study, with 8 subjects in cohorts 7 **to** 9 and **up to** 20 subjects in cohort 10. **Up to 6 subjects per cohort will be enrolled in cohorts 12 and 13.** Additional subjects may be enrolled if a DLRT recommendation is made to expand, repeat, or add cohorts to the study **or if replacement subjects are added**.

Summary of Subject Eligibility Criteria

Subjects in the study will be males and females ≥ 18 to ≤ 65 years of age at the time of randomization with a body mass index (BMI) of ≥ 30.0 kg/m^2 and ≤ 40.0 kg/m^2**.** Females enrolled must be of nonreproductive potential.

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

Treatments

Cohorts 1 to 6 and cohort 11 (Part A): After completion of all predose procedures on the day of dosing, subjects in cohorts 1 to 5 and cohort 11 will receive AMG 133 (21 mg or a dose based on available data from previous cohorts, not exceeding 70, 140, 280, 560, or 840 mg), or placebo SC on day 1. For cohort 6, subjects will receive AMG 133 at a dose based on available data from previous cohorts, not exceeding 70 mg or placebo IV on day 1.

Cohorts 7 to 9 (Part B): After completion of all predose procedures on the day of dosing, subjects will receive AMG 133 (a dose based on available data from previous cohorts, not exceeding 140, 280, and 560 mg for cohorts 7, 8, and 9 respectively), or placebo SC on days 1, 29, and 57.

Cohort 10 (Part B): After completion of all predose procedures on the day of dosing, subjects will then receive placebo or AMG 133 at a dose level not exceeding 560 mg or placebo SC Q4W on days 1, 29, 57 in addition to the [redacted] The dose level of cohort 10 will be determined based on the emerging safety and PK data of the preceding cohorts and will not exceed the highest dose evaluated in cohorts 7 **to** 9.

Cohorts 12 to 13 (Part C): After completion of all predose procedures on the day of dosing, subjects will receive AMG 133 [redacted] mg SC on day [redacted] Subjects enrolled in cohort 12 will also receive [redacted] mg SC on day [redacted] followed by a dose of [redacted] mg SC on days [redacted] Subjects enrolled into cohort 13 will also receive [redacted] mg SC on days [redacted] followed by a dose of [redacted] mg on days [redacted]

Planned Dose Levels by Cohort

	Cohort	No. Subjects	AMG 133/Placebo Dose/ Frequency	Route	N (active: placebo)
Part A	1	8	21 mg day 1	SC	6:2
	2	8	Not exceeding 70 mg day 1[a]	SC	6:2
	3	8	Not exceeding 140 mg day 1[a]	SC	6:2
	4	8	Not exceeding 280 mg day 1[a]	SC	6:2
	5	8	Not exceeding 560 mg day 1[a]	SC	6:2
	11	8	Not exceeding 840 mg day 1[a]	SC	6:2
	6	8	Not exceeding 70 mg day 1[a]	IV	6:2
Part B	7	8	Not exceeding 140 mg[b] Q4W x 3	SC	6:2
	8	8	Not exceeding 280 mg[b] Q4W x 3	SC	6:2
	9	8	Not exceeding 560 mg[b] Q4W x 3	SC	6:2
	10	≤ 20	Not exceeding 560 mg[c] Q4W x 3 + [redacted]	SC	≤ 15:5
Part C	**12**	**≤ 6**	[redacted]	**SC**	**N/A**
	13	**≤ 6**		**SC**	**N/A**

QW = every week; Q4W = every four weeks; SC = subcutaneous; IV = intravenous.
[a] Actual dose levels will be based on available data from previous cohorts.
[b] Dose will not exceed the highest dose evaluated in cohorts 1 to 5 and cohort 11 (Part A)
[c] Dose will not exceed the highest dose evaluated in cohorts 7 **to** 9 (Part B)

Procedures

Screening

For all subjects, after informed consent is obtained, all screening procedures and tests establishing eligibility will be performed within 28 days before the first dose of AMG 133 or placebo (day 1).

Study procedures are summarized in the Schedule of Activities **(Section 1.3)**.

Serious adverse events will be collected from the time the informed consent form is signed.

Day -28 to -14 (Part B)

Cohort 10: Subjects who meet all the screening inclusion/exclusion criteria will be eligible to report to the research facility prior to day -14. [redacted]

[redacted]

Day -28 to -4 (Part B):

Cohorts 7 **to** 9: Subjects who meet all the screening inclusion/exclusion criteria will be eligible to report to the research facility on or prior to day -4 **depending on scheduling allowances**, [redacted]

In-House Residency

Subjects in cohorts 1 to 5 and cohort 11 (Part A) will be admitted after confirmed eligibility on day -2 for a 10-day (9-night) residency period. Subjects in cohort 6 (Part A) will be admitted after confirmed eligibility on day -2 for an 8-day (7-night) residency period.

Subjects in cohorts 7 **to** 10 (Part B) will be admitted after confirmed eligibility on day **-**1 for a 3 day (2 night) residency. Subjects will be dosed on day 1, the second day of residency. Subjects will be admitted on days 28 – 30 and days 56 – 58 for a 3 day (2 night) residency. Subjects will receive AMG 133 or placebo on days 29 and 57, respectively.

Subjects in cohorts 12 and 13 (Part C) will have an optional overnight in-house residency period after the scheduled [redacted] mg SC AMG 133 administration on days [redacted] for cohort 12 and on days [redacted] for cohort 13. Subjects may remain in-house for continued observation based on changes in the vital signs and/or the subject reports adverse events that interfere with daily activities and/or per clinical judgement of the site Principal Investigator if the subject is anticipated to require supportive management of adverse events. Subjects in cohorts 12 and 13 will be admitted for a required overnight observation on either Day 15 (cohort 12) or Day 29 (cohort 13) after receiving the first dose of [redacted] mg SC AMG 133.

Day -2 Part A; Part C

Part A: Cohorts 1 **to** 6 and cohort 11: Subjects who meet all the screening inclusion criteria and none of the exclusion criteria will be eligible to report to the research facility on day -2, at which time assessments will be performed to confirm eligibility. If subjects are eligible after the completion of all day -2 assessments, subjects will be randomized to receive either AMG 133 or placebo on day 1.

Part C: Cohorts 12 - 13: Subjects who meet all the screening inclusion criteria and none of the exclusion criteria will be eligible to report to the research facility once on day -2 (up to day -4), at which time assessments will be performed to confirm eligibility. If subjects are eligible after the completion of all day -2 assessments, subjects will receive AMG 133 on day 1.

Day -1

Part A: Cohorts 1 to 5 and cohort 11: A [redacted] test will be performed on day -1 along with additional procedures as outlined in the Schedule of Activities in **Section 1.3**. As part of the [redacted]

summarized in the Schedule of Activities in **Section 1.3**. [redacted] tests will not be performed in cohort 6.

Part B: cohorts 7 **to** 10: Subjects who meet all the screening inclusion criteria and none of the exclusion criteria will be eligible to report to the research facility on day -1, at which time assessments will be performed to confirm eligibility. If subjects are eligible after the completion of all day 1 assessments, subjects will be randomized to receive either AMG 133 or placebo on day 1.

Day 1:

Part A: After completion of all predose procedures on the day of dosing (day 1), subjects will receive investigational product (SC for cohorts 1 to 5 and cohort 11 and IV for cohort 6, only). Subjects will undergo vital signs and pharmacokinetics blood draws postdose as outlined in the Schedule of Activities in **Section 1.3**.

Part B: After completion of all predose procedures on the day of dosing (day 1), subjects will receive investigational product (SC for cohorts 7 **to**10). Subjects should undergo additional vital sign assessments 3 hours after dosing but are not scheduled to get postdose blood draws on day 1 (**see Schedule of Activities in Section 1.3**).

Part C: After completion of all predose procedures on the day of dosing (day 1), subjects will receive AMG 133 (SC). Subjects are scheduled to get postdose blood draws on day 1 but should undergo additional monitoring (per clinical site standard operating procedures) and vital sign assessments approximately 4 to 5 hours after dosing. The subjects can be discharged from the clinical facility based upon a stable vital signs and assessment per clinical site standard operating procedures.

Day 7

Cohorts 1 to 5 and cohort 11: A [redacted] test will be repeated on day 7 along with additional procedures as outlined in the Schedule of Activities in **Section 1.3**. [redacted] tests will not be performed in cohort 6.

Treatment and Follow-Up

Part A: AMG 133 or placebo will be administered SC on day 1 after predose procedures.

Part B: AMG 133 or placebo will be administered SC Q4W x3 on days 1, 29, and 57 after predose procedures.

Part C: After predose procedures for cohort 12, [redacted] mg AMG 133 will be administered SC on days [redacted] and [redacted] mg will be administered SC on days [redacted] After predose procedures for cohort 13, [redacted] mg AMG 133 will be administered SC on days [redacted] mg will be administered SC on days [redacted]

All procedures on day of dosing as outlined in the Schedule of Activities (**Section 1.3**) should occur prior to dosing of AMG 133 or placebo unless otherwise specified.

Subjects will return to the research facility as outlined in the Schedule of Activities in **Section 1.3** and will undergo the following assessments at specified time points throughout the study: physical examinations, physical measurements, 12-lead ECGs, vital sign measurements, adverse event and serious adverse event collection, concomitant therapies review, clinical laboratory evaluations, [redacted] pharmacokinetic and other pharmacodynamic assessments. Specific assessments for Part A cohorts 1 to 5 and cohort 11 include the [redacted] test and specific

assessments for Part B **and Part C** (cohorts 7 **to 13**) include the Patient Health Questionnaire-9 (PHQ-9), Columbia Suicide Severity Rating Scale (C-SSRS), [redacted] Subjects will remain in the research facility until completion of all study procedures on each visit day.

End of Study (EOS):

Subjects will be followed through the completion of end of study (EOS) procedures on day 150 ± 7 (Part A)**,** day 207 ± 7 (Part B)**, and up to day 207 ± 7 (Part C).**

All adverse events and use of concomitant medication will be collected for the duration of the study, up to and including the **EOS** visit. All treatment-emergent adverse events or laboratory abnormalities will be followed until either: a) resolution of the abnormality, b) it is considered stable in the opinion of the investigator, or c) subject is lost to follow-up.

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in **Section 1.3**.

Statistical Considerations

Descriptive statistics will be provided for selected demographics, safety, pharmacokinetic, and pharmacodynamic endpoints. Accumulating pharmacodynamic data might be reviewed throughout the study by treatment periodically.

Descriptive statistics on continuous measurements will include means, medians, 25th and 75th percentiles, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Pharmacokinetic, pharmacodynamic, and clinical laboratory data will be summarized by treatment group and at each time point when samples are collected. Graphical summaries of the data may also be presented. The number and percentage of subjects reporting any treatment-emergent adverse events will be tabulated by system organ class and preferred term and will be further classified by relationship to investigational product.

The sample size for the study is based on practical considerations. No statistical hypotheses will be tested. For safety considerations, with up to **87** subjects (42 subjects from cohorts 1 to 6 and cohort 11 of Part A, 18 subjects from cohorts 7 to 9 of Part B**, up to** 15 subjects from cohort 10 of Part B**, and up to 12 subjects in Part C**) receiving AMG 133, there is at least **92.9**% chance of detecting an adverse event with a true incidence rate of 3% or greater and at least **98.8**% chance of detecting an adverse event with a true incidence rate of 5% or greater.

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

Statistical Hypotheses

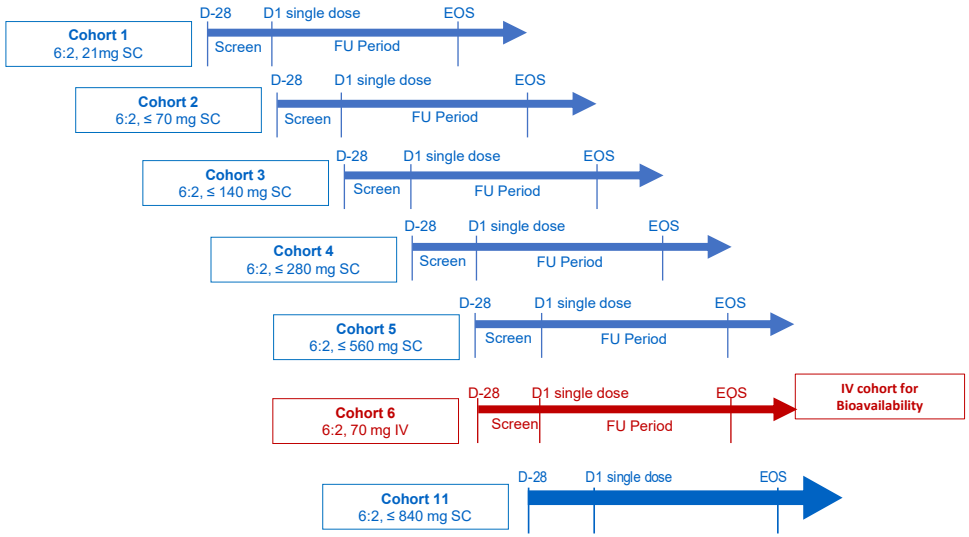
No statistical hypotheses will be tested in this study.

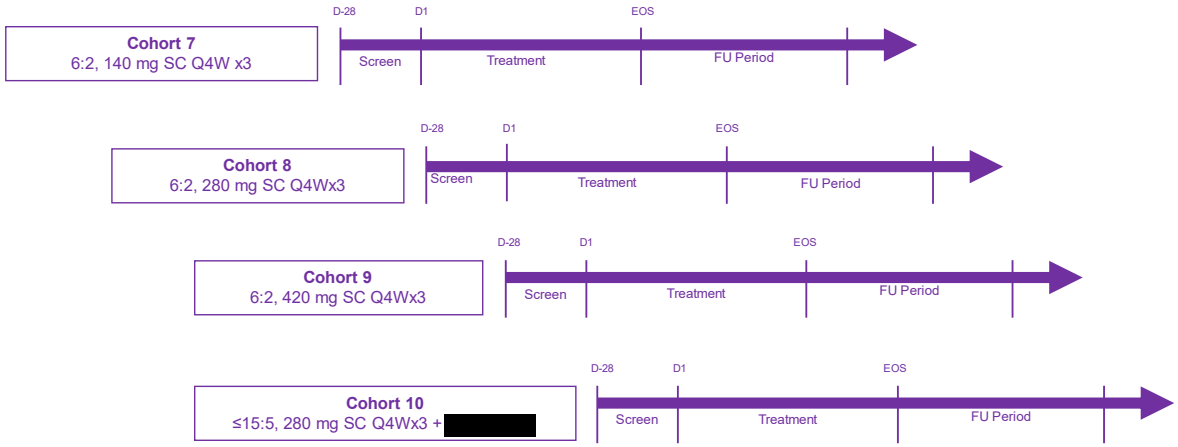
Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-2. Study Schema

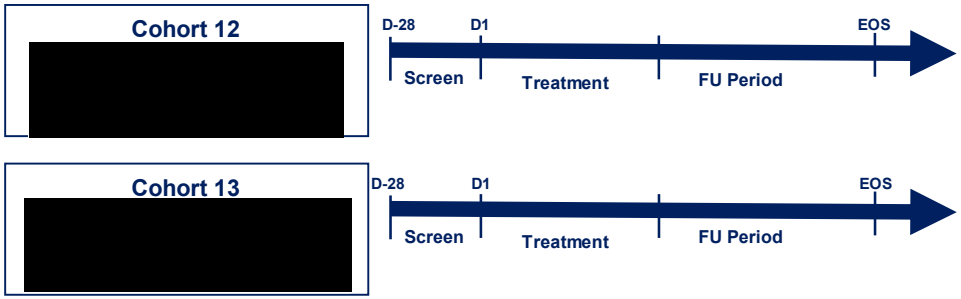
Part A: Single Ascending Dose in Obese Subjects (n = 56)





D = day; EOS = end of study; FU = follow-up; IV = intravenous; **Q4W = every 4 weeks;** SC = subcutaneous.

Part C: Modified Dose-escalation in Obese Subjects (n ≤ 12)



D = day; FU = follow-up; SC = subcutaneous.

1.3 Schedule of Activities (SoA)

Table 1. Schedule of Activities — Cohorts 1 to 5 and Cohort 11

	Screening (Days)			Treatment Period (Days)															EOS/ SFU[a]	Notes
PROCEDURE	**-28**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15 ± 1**	**22 ± 1**	**29 ± 1**	**43 ± 3**	**57 ± 3**	**71 ± 3**	**92 ± 7**	**120 ± 7**	**150 ± 7**	**In-house residency day -2 to 8**
GENERAL AND SAFETY ASSESSMENTS																					
Informed consent	X																				
Inclusion and exclusion criteria	X																				
Demographics	X																				
Physical examination	X	X			X					X				X		X		X			
Physical measurements	X			X[b,c]					X[b]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Medical history	X																				
Substance use history	X																				
ECG triplicate measurement[d]	X[e]	X[e]		X[c,f]					X		X			X		X			X	X	
Vital signs	X	X	X	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
LABORATORY ASSESSMENTS																					
Serum and/or Urine pregnancy test (females only)[g,h]	X	X																		X	Serum pregnancy test at day -28 and EOS, urine pregnancy test at day -2
Serum FSH test[h] (postmenopausal females only)	X																				For postmenopausal status confirmation
Coagulation[h]	X	X																			
Hematology[h]	X	X			X						X	X		X		X		X	X	X	
Chemistry[h,j]	X	X			X						X	X		X		X		X	X	X	Calcitonin and TSH at day -28 only. Serum amylase and lipase on days -2, 8, 15, 29, and EOS only.

Page 1 of 3

Footnotes defined on last page of the table.

Table 1. Schedule of Activities — Cohorts 1 to 5 and Cohort 11

	Screening (Days)			Treatment Period (Days)																EOS/ SFU[a]	Notes
PROCEDURE	**-28**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15 ± 1**	**22 ± 1**	**29 ± 1**	**43 ± 3**	**57 ± 3**	**71 ± 3**	**92 ± 7**	**120 ± 7**	**150 ± 7**	**In-house residency day -2 to 8**
LABORATORY ASSESSMENTS																					
HIV, Hepatitis B and C screening[h]	X																				
[redacted]																					
eGFR[h]	X	X																			
Urinalysis[h]	X	X									X			X						X	
Alcohol, cotinine, and drug screen[h]	X	X																			
Anti-AMG 133-antibody[i]				X[c]								X		X		X			X	X	
Creatine Kinase	X	X		X	X						X			X		X		X	X	X	
STUDY-SPECIFIC ASSESSMENTS (eg, DISEASE-SPECIFIC ASSESSMENTS, RADIOLOGICAL ASSESSMENTS)																					
[redacted]																					
PHARMACOKINETIC ASSESSMENTS																					
Plasma AMG 133 pharmacokinetics[i]				X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sampling time points on day 1 to include predose, and at 1, 2, 4, and 8 hours postdose.
[redacted]																					

Footnotes defined on last page of the table.

Table 1. Schedule of Activities — Cohorts 1 to 5 and Cohort 11

	Screening (Days)			Treatment Period (Days)																EOS/ SFU[a]	Notes
PROCEDURE	**-28**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15 ± 1**	**22 ± 1**	**29 ± 1**	**43 ± 3**	**57 ± 3**	**71 ± 3**	**92 ± 7**	**120 ± 7**	**150 ± 7**	**In-house residency day -2 to 8**
PHARMACODYNAMIC ASSESSMENTS																					
[redacted]																					
PHARMACOGENETIC ASSESSMENTS																					
Pharmacogenetic studies[l]			X																		
STUDY TREATMENT																					
Amgen investigational product				X																	

ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study;FSH = follicle stimulating hormone; [redacted] HIV = human immunodeficiency virus; SFU = safety follow-up.

[a] Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the end of the last dosing interval of investigational product.

[b] Body weight **(kg)** only.

[c] Predose assessment.

[d] 12-lead ECGs to be performed in a standardized method, in triplicate, and run consecutively (all 3 ECGs should be completed within a total of 5 minutes from start of the first to the completion of the third).

[e] Single 12-lead ECG.

[f] 3 sets of triplicate 12-lead ECGs at baseline (day 1 predose).

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

[h] Analyzed at the local laboratory, additional samples may be collected for safety reasons, at the investigator's discretion.

[i] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons, at the investigator's discretion.

[j] 10-hour fasting is required at all time points [redacted]

[k] Local laboratory at screening, then central laboratory at other time points.

[l] For subjects who provided informed consent for the pharmacogenetic studies.

Table 2. Schedule of Activities — Cohort 6

	Screening (Days)			Treatment Period (Days)														EOS/ SFU[a]	Notes
PROCEDURE	**-28**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**15 ± 1**	**22 ± 1**	**29 ± 1**	**43 ± 3**	**57 ± 3**	**71 ± 3**	**92 ± 7**	**120 ± 7**	**150 ± 7**	**In-house residency day -2 to 6**
GENERAL AND SAFETY ASSESSMENTS																			
Informed consent	X																		
Inclusion and exclusion criteria	X																		
Demographics	X																		
Physical examination	X	X			X				X			X		X		X		X	
Physical measurements	X			X[b,c]					X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Medical history	X																		
Substance use history	X																		
ECG triplicate measurement[d]	X[e]	X[e]		X[c,f]	X				X			X		X			X	X	ECG on day 1 should be performed predose and at 10 minutes and 2 hours postdose.
Vital signs	X	X	X	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Vital signs on day 1 to be measured predose, and at 2, 4, and 8 hours postdose.
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
LABORATORY ASSESSMENTS																			
Serum and/or Urine pregnancy test (females only)[g,h]	X	X																X	Serum pregnancy test at day -28 and EOS, urine pregnancy test at day -2
Serum FSH test[h] (postmenopausal females only)	X																		For postmenopausal status confirmation
Coagulation[h]	X	X																	

Page 1 of 3

Footnotes defined on last page of the table.

Table 2. Schedule of Activities — Cohort 6

	Screening (Days)			Treatment Period (Days)														EOS/ SFU	Notes
PROCEDURE	**-28**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**15 ± 1**	**22 ± 1**	**29 ± 1**	**43 ± 3**	**57 ± 3**	**71 ± 3**	**92 ± 7**	**120 ± 7**	**150 ± 7**	**In-house residency day -2 to 6**
LABORATORY ASSESSMENTS																			
Hematology[h]	X	X		X	X				X	X		X		X		X	X	X	Hematology at day 1 should be collected 2 hours postdose.
Chemistry[h,j]	X	X		X	X				X	X		X		X		X	X	X	Chemistry at day 1 should be collected 2 hours postdose. Calcitonin and TSH at day -28 only. Serum amylase and lipase on days -2, 6, 15, 29 and EOS only.
HIV, Hepatitis B and C screening[h]	X																		
[redacted]																			
eGFR[h]	X	X																	
Urinalysis[h]	X	X							X			X						X	
Alcohol, cotinine, and drug screen[h]	X	X																	
Anti-AMG 133-antibody[i]				X[c]						X		X		X			X	X	
Creatine Kinase	X	X		X	X				X			X		X		X	X	X	
STUDY-SPECIFIC ASSESSMENTS (eg, DISEASE-SPECIFIC ASSESSMENTS, RADIOLOGICAL ASSESSMENTS)																			
[redacted]																			
PHARMACOKINETIC ASSESSMENTS																			

Footnotes defined on last page of the table.

Table 2. Schedule of Activities — Cohort 6

	Screening (Days)			Treatment Period (Days)														EOS/ SFU	Notes
PROCEDURE	**-28**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**15 ± 1**	**22 ± 1**	**29 ± 1**	**43 ± 3**	**57 ± 3**	**71 ± 3**	**92 ± 7**	**120 ± 7**	**150 ± 7**	**In-house residency day -2 to 6**
Plasma AMG 133 pharmacokinetics[i]				X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sampling time points on day 1 to include predose, and at 10 minutes and 1, 2, 4, and 8 hours postdose.
PHARMACODYNAMIC ASSESSMENTS																			
[redacted]																			
PHARMACOGENETIC ASSESSMENTS																			
Pharmacogenetic studies[l]			X																
STUDY TREATMENT																			
Amgen investigational product				X															

ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle stimulating hormone; [redacted] HIV = human immunodeficiency virus; SFU = safety follow-up.

[a] Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the end of the last dosing interval of investigational product.

[b] Body weight **(kg)** only.

[c] Predose assessment.

[d] 12-lead ECGs to be performed in a standardized method, in triplicate, and run consecutively (all 3 ECGs should be completed within a total of 5 minutes from start of the first to the completion of the third).

[e] Single 12-lead ECG.

[f] 3 sets of triplicate 12-lead ECGs at baseline (day 1 predose) followed by triplicate 12-lead ECGs at 10 minutes and 2 hours postdose.

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

[h] Analyzed at the local laboratory, additional samples may be collected for safety reasons, at the investigator's discretion.

[i] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons, at the investigator's discretion.

[j] 10-hour fasting is required at all time points.

[k] Local laboratory at screening, then central laboratory at other time points.
[l] For subjects who provided informed consent for the pharmacogenetic studies.

Table 3. Schedule of Activities – Cohorts 7 to 9

PROCEDURE	Screening			Treatment Period																	EOS/SFU[a]						Notes
Study Day	-28	-4	-1	1	4	5	7	15	22	29	36	43	50	57	60	61	63	71	78	84	85	87	127	169	207		
Visit Windows								± 1 day			± 1 day					± 1 day				± 2 day			± 7 day				
GENERAL AND SAFETY ASSESSMENTS																											
Informed consent	X																										
Inclusion and exclusion criteria	X																										
Demographics	X																										
Medical history	X																										
Substance use history	X																										
Physical examination[b]	X		X							X[c]				X[c]							X		X		X		
Height and body mass index	X																										
Body weight **(kg)**	X			X[c]			X	X	X	X[c]	X	X	X	X[c]			X	X	X		X		X	X	X		
Waist circumference **(cm)**				X[c]						X[c]				X[c]							X		X		X		
C-SSRS + PHQ9	X		X							X[c]				X[c]													
ECG triplicate measurement[d]	X[e]		X[e]	X[c,f]						X[c]				X[c]							X				X		
Vital signs (BP, HR, RR, Temp)	X	X	X	X[c,g]		X	X	X	X	X[c,g]	X	X	X	X[c,g]		X	X	X	X		X		X	X	X		
Adverse events				X		X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X	X		
Serious adverse events	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X	X		
Concomitant therapies review	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X	X		
STUDY TREATMENT																											
Amgen investigational product				X						X				X													
LABORATORY ASSESSMENTS																											
Coagulation[h]	X		X																								
Hematology[h]	X		X					X		X[c]				X[c]		X	X				X		X	X	X		
Chemistry[h,i]	X		X					X		X[c]				X[c]		X	X				X		X	X	X		
HIV, Hepatitis B and C screening[h]	X																										
[redacted]																											
Serum amylase and lipase[i]			X				X			X	X			X		X	X						X	X	X		
eGFR[h]	X		X																						X		
Urinalysis[h]	X		X																		X				X		
Alcohol, cotinine, and drug screen[h]	X		X																								
Serum and/or Urine pregnancy test (females only)[h,j]	X		X																						X		
Serum FSH test[h] (postmenopausal females only)	X																										

Footnotes defined on last page of the table.

Table 3. Schedule of Activities – Cohorts 7 to 9

PROCEDURE	Screening			Treatment Period																EOS/SFU[a]						Notes
Study Day	-28	-4	-1	1	4	5	7	15	22	29	36	43	50	57	60	61	63	71	78	84	85	87	127	169	207	
Visit Windows								± 1 day			± 1 day					± 1 day				± 2 day			± 7 day			
STUDY-SPECIFIC ASSESSMENTS (eg, DISEASE-SPECIFIC ASSESSMENTS, RADIOLOGICAL ASSESSMENTS)																										
Anti-AMG 133-antibody[k]				X[c]				X		X[c]				X[c]							X				X	
[redacted]																										
PHARMACOKINETIC ASSESSMENTS																										
Plasma AMG 133 pharmacokinetics[k]				X[c]		X	X	X	X	X[c]	X	X	X	X[c]		X	X	X	X		X		X	X	X	
PHARMACODYNAMIC ASSESSMENTS																										
[redacted]																										
PHARMACOGENETIC ASSESSMENTS																										
Pharmacogenetic studies[k,n]			X																							
IMAGING																										
[redacted]																										

Page 2 of 2

BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]
ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = follicle stimulating hormone; [redacted]
HIV = human immunodeficiency virus; HR = heart rate; PD = pharmacodynamic; PHQ9 = Patient Health Questionnaire-9;
RR = respiratory rate; SFU = safety follow-up; Temp = temperature.
Please note: Subjects will be admitted after confirmed eligibility on day -1 for a 3 day (2 night) residency. Subjects will be dosed on day 1, the second day of residency. Subjects will be admitted on days 28 – 30 and days 56 – 58 for a 3 day (2 night) residency. Subjects will receive AMG 133 or placebo on days 29 and 57, respectively.

[a] Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the end of the last dosing interval of investigational product.
[b] Physical exam to include neurologic assessment.
[c] Predose assessment.
[d] 12-lead ECGs to be performed in a standardized method, in triplicate, and run consecutively (all 3 ECGs should be completed within a total of 5 minutes from start of the first to the completion of the third).
[e] Single 12-lead ECG.
[f] 3 sets of triplicate 12-lead ECGs at baseline (day 1 predose).

[g] Subjects should get vital signs 3 hours after dosing
[h] Analyzed at the local laboratory, additional samples may be collected for safety reasons, at the investigator's discretion.
[i] 10-hour fasting is required at all time points.
[j] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
[k] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons, at the investigator's discretion.

[redacted]

[m] Local laboratory at screening, then central laboratory at other time points.
[n] For subjects who provided informed consent for the pharmacogenetic studies

[redacted]

Table 4. Schedule of Activities – Cohort 10

PROCEDURE	Screening			Treatment Period														EOS/SFU[a]					Notes
Study Day	-28	-14	-1	1	5	7	15	22	29	36	43	50	57	63	71	78	85	127	155	169	207	
Visit Windows					± 1 day					± 1 day				± 1 day			± 3 day		± 7 day			
GENERAL AND SAFETY ASSESSMENTS																						
Informed consent	X																					
Inclusion and exclusion criteria	X																					
Demographics	X																					
Medical history	X																					
Substance use history	X																					
Physical examination[b]	X		X						X[c]				X[c]				X	X			X	
Height and body mass index	X																					
Body weight **(kg)**	X			X[c]		X	X	X	X[c]	X	X	X	X[c]	X	X	X	X	X		X	X	
Waist circumference **(cm)**				X[c]					X[c]				X[c]				X	X			X	
C-SSRS + PHQ9	X		X						X[c]				X[c]									
ECG triplicate measurement[d]	X[e]		X[e]	X[c,f]					X[c]				X[c]				X				X	
Vital signs (BP, HR, RR, Temp)	X		X	X[c, p]	X	X	X	X	X[c,p]	X	X	X	X[c,p]	X	X	X	X	X		X	X	
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Serious adverse events	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Concomitant therapies review	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
STUDY TREATMENT																						
Amgen investigational product				X					X				X									
LABORATORY ASSESSMENTS																						
Coagulation[g]	X		X																			
Hematology[g]	X		X				X		X[c]				X[c]	X			X	X		X	X	
Chemistry[g,h]	X		X				X		X[c]				X[c]	X			X	X		X	X	
HIV, Hepatitis B and C screening[g]	X																					
[redacted]																						
Serum amylase and lipase[h]			X			X			X	X			X	X				X		X	X	
eGFR[g]	X		X																		X	
Urinalysis[g]	X		X														X				X	
Alcohol, cotinine, and drug screen[g]	X		X																			
Serum and/or Urine pregnancy test (females only)[g,i]	X		X																		X	
Serum FSH test[g] (postmenopausal females only)	X																					

Footnotes defined on last page of the table.

Table 4. Schedule of Activities – Cohort 10

PROCEDURE	Screening			Treatment Period													EOS/SFU[a]					Notes
Study Day	**-28**	**-14**	**-1**	**1**	**5**	**7**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**63**	**71**	**78**	**85**	**127**	**155**	**169**	**207**	
Visit Windows					**± 1 day**					**± 1 day**				**± 1 day**			**± 3 day**		**± 7 day**			
Anti-AMG 133-antibody[j]				X[c]			X		X[c]				X[c]				X				X	
STUDY-SPECIFIC ASSESSMENTS (eg, DISEASE-SPECIFIC ASSESSMENTS, RADIOLOGICAL ASSESSMENTS)																						
[redacted]																						
PHARMACOKINETIC ASSESSMENTS																						
Plasma AMG 133 pharmacokinetics[j]				X[c]	X	X	X	X	X[c]	X	X	X	X[c]	X	X	X	X			X	X	
PHARMACODYNAMIC ASSESSMENTS																						
[redacted]																						
PHARMACOGENETIC ASSESSMENTS																						
Pharmacogenetic studies[j,n]			X																			
IMAGING																						
[redacted]																						

BP= blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]
ECG = electrocardiogram; eGFR =estimated glomerular filtration rate; EOS = end of study; [redacted] ; FSH = follicle stimulating hormone; [redacted] HIV = human immunodeficiency virus; HR = heart rate [redacted]
PD = pharmacodynamic; PHQ9 = Patient Health Questionnaire-9; RR = respiratory rate; SFU = safety follow-up; Temp = temperature.
Please note: Subjects will be admitted after confirmed eligibility on day -1 for a 3 day (2 night) residency. Subjects will be dosed on day 1, the second day of residency. Subjects will be admitted on days 28 – 30 and days 56 – 58 for a 3 day (2 night) residency. Subjects will receive AMG 133 or placebo on days 29 and 57, respectively.
[a] Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the end of the last dosing interval of investigational product.
[b] Physical exam to include neurologic assessment.
[c] Predose assessment.

[d] 12-lead ECGs to be performed in a standardized method, in triplicate, and run consecutively (all 3 ECGs should be completed within a total of 5 minutes from start of the first to the completion of the third).
[e] Single 12-lead ECG.
[f] 3 sets of triplicate 12-lead ECGs at baseline (day 1 predose).
[g] Analyzed at the local laboratory, additional samples may be collected for safety reasons, at the investigator's discretion.
[h] 10-hour fasting is required at all time points.
[i] Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
[j] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons, at the investigator's discretion.
[redacted]
[m] Local laboratory at screening, then central laboratory at other time points.
[n] For subjects who provided informed consent for the pharmacogenetic studies.
[redacted]
[p] Subjects should get vital signs 3 hours after dosing

Table 5. Schedule of Activities – Part C Cohort 12

PROCEDURE	SCREENING		TREATMENT PERIOD							SFU/EOSA	
Study Day	**-28**	**-2[b]**	**1**	**8**	**15**	**20**	**43**	**57**	**71**	**132**	**193**
Visit Windows						**± 1 day**		**± 3 days**		**±7 days**	
Visit type	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**P**	**C**	**P**	**C**
GENERAL AND SAFETY ASSESSMENTS											
Informed consent	**X**										
Inclusion and exclusion criteria	**X**										
Demographics	**X**										
Medical history	**X**										
Substance use history	**X**										
Physical examination[c]	**X**	**X**					**X**		**X**		**X**
Height and body mass index	**X**										
Body weight (kg)	**X**		**X[d]**	**X[d]**	**X[d]**	**X**	**X[d]**		**X**		**X**
Waist circumference (measured in cm only)			**X[d]**				**X[d]**		**X**		**X**
C-SSRS + PHQ9	**X**		**X[d]**	**X[d]**	**X[d]**		**X[d]**		**X**		**X**
ECG triplicate measurement	**X[e]**	**X[e]**	**X[d,f,g]**				**X[d,f]**		**X[f]**		
Vital signs (BP, HR, RR, Temp)	**X**	X	**X[d,h]**	**X[d,h]**	**X[d,h]**	**X**	**X[d,h]**		**X**		**X**
Adverse events			**X**	**X**	**X**	**X**	**X**	**X[i]**	**X**	**X[i]**	**X**
Serious adverse events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X[i]**	**X**	**X[i]**	**X**
Concomitant therapies review	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X[i]**	**X**	**X[i]**	**X**

STUDY TREATMENT											
Amgen investigational product	[redacted]										
LABORATORY ASSESSMENTS											
Coagulation[j]	X	X									
Hematology[j]	X	X		X	X	X	X		X		X
Chemistry[j]	X	X		X	X	X	X		X		X
HS-CRP[j]			X						X		X
HIV, Hepatitis B and C screening[j]	X										
[redacted]											
Serum amylase and lipase[j]			X	X	X	X	X		X		X
eGFR[j]	X	X									X
Urinalysis[j]	X	X							X		X
Alcohol, cotinine, and drug screen[j]	X	X									

Page 1 of 2

Footnotes defined on last page of the table.

Table 5. Schedule of Activities – Part C Cohort 12

PROCEDURE	SCREENING		TREATMENT PERIOD							SFU/EOSA	
Study Day	-28	-2[b]	1	8	15	20	43	57	71	132	193
Visit Windows						± 1 day		± 3 days		± 7 days	
Visit type	C	C	C	C	C	C	C	P	C	P	C
Serum and/or Urine pregnancy test (females only)[j]	X	X									X
Serum FSH test[j] (postmenopausal females only)	X										
Anti-AMG 133-antibody[k,m]			X[d]		X[d]		X[d]		X		X
STUDY-SPECIFIC ASSESSMENTS (eg, DISEASE-SPECIFIC ASSESSMENTS, RADIOLOGICAL ASSESSMENTS)											
[redacted]											
PHARMACOKINETIC ASSESSMENTS											
Plasma AMG 133 pharmacokinetics[k,m]			X[d]	X[d]	X[d]		X[d]		X		X
PHARMACODYNAMIC ASSESSMENTS											
[redacted]											

PHARMACOGENETIC ASSESSMENTS											
Pharmacogenetic studies[o,m]		X									
IMAGING											
[redacted]											

BP = blood pressure; C = clinic visit; C-SSRS = Columbia Suicide Severity Rating Scale; cm = centimeters; [redacted]; [redacted]; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; [redacted] FSH = follicle stimulating hormone; [redacted] HIV = human immunodeficiency virus; HR = heart rate; HS-CRP = high-sensitivity C-reactive protein; [redacted] P = phone visit; PD = pharmacodynamic; PHQ9 = Patient Health Questionnaire-9; RR = respiratory rate; [redacted]; SFU = safety follow-up; Temp = temperature.

Please note: Subjects are eligible for an optional in-house residence period on Day 1 and 8 for an overnight observation period. Subjects are eligible for a required in-house residency period for Day 15 and 43. Subjects will receive AMG 133 on Days 1, 8, 15, and 43.

[a] Upon permanent discontinuation from the study treatment for any reason, an SFU visit will be performed approximately 30 (+3) days after the end of the last dosing interval of investigational product.
[b] Eligibility can be confirmed up to -4 days prior to Day 1 to allow for lab tests to result.
[c] Physical exam to include neurologic assessment.
[d] Predose assessment
[e] Single 12-lead ECG
[f] 12-lead ECGs to be performed in a standardized method, in triplicate, and run consecutively (all 3 ECGs should be completed within a total of 5 minutes from start of the first to the completion of the third).
[g] 3 sets of triplicate 12-lead ECGs at baseline (Day 1 predose)
[h] Subjects should get vital signs 4 to 5 hours after dosing
[i] Phone call follow up
[j] Analyzed at the local laboratory, additional samples may be collected for safety reasons, at the investigator's discretion.
[k] 10-hour fasting is required at all time points.
[l] Additional on-treatment pregnancy testing may be performed at the investigator's discretion, if there is suspicion that a female subject is pregnant or per local laws and regulations.
[m] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons, at the investigator's discretion.
[n] Local laboratory at screening, then central laboratory at other time points.
[o] For subjects who provided informed consent for the pharmacogenetic studies.
[redacted]

Table 6. Schedule of Activities - Part C Cohort 13

PROCEDURE	SCREENING		TREATMENT PERIOD									SFU/EOSA	
Study Day	-28	-2[b]	1	8	15	22	29	34	57	64	85	146	207
Visit Windows								± 1 day		± 3 days		± 7 days	
Visit type	C	C	C	C	C	C	C	C	C	P	C	P	C

GENERAL AND SAFETY ASSESSMENTS													
Informed consent	X												
Inclusion and exclusion criteria	X												
Demographics	X												
Medical history	X												
Substance use history	X												
Physical examination[c]	X	X					X				X		X
Height and body mass index	X												
Body weight (kg)	X		X[d]	X[d]	X[d]	X[d]	X[d]	X	X[d]		X		X
Waist circumference (measured in cm only)			X[d]				X[d]		X[d]		X		X
C-SSRS + PHQ9	X		X[d]	X[d]	X[d]	X[d]	X[d]		X[d]		X		X
ECG triplicate measurement	X[e]	X[e]	X[d,f,g]				X[d,f]		X[d,f]		X[f]		
Vital signs (BP, HR, RR, Temp)	X	X	X[d,h]	X[d,h]	X[d,h]	X[d,h]	X[d,h]	X	X[d,h]		X		X
Adverse events			X	X	X	X	X	X	X	X[i]	X	X[i]	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X[i]	X	X[i]	X
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X[i]	X	X[i]	X
STUDY TREATMENT													
Amgen investigational product	[redacted]												
LABORATORY ASSESSMENTS													
Coagulation[j]	X	X											
Hematology[j]	X	X		X	X	X	X	X	X		X		X
Chemistry[j]	X	X		X	X	X	X	X	X		X		X
HS-CRP[j]			X						X		X		X
HIV, Hepatitis B and C screening[j]	X												
[redacted]													
Serum amylase and lipase[j]			X	X	X	X	X	X	X		X		X
eGFR[j]	X	X											X
Urinalysis[j]	X	X									X		X
Alcohol, cotinine, and drug screen[j]	X	X											
Serum and/or Urine pregnancy test (females only)[j]	X	X											X

Page 1 of 2

Footnotes defined on last page of the table.

Table 6. Schedule of Activities - Part C Cohort 13

PROCEDURE	SCREENING		TREATMENT PERIOD									SFU/EOSA	
Study Day	-28	-2[b]	1	8	15	22	29	34	57	64	85	146	207

Visit Windows								± 1 day		± 3 days		± 7 days	
Visit type	C	C	C	C	C	C	C	C	C	P	C	P	C
Serum FSH test[j] (postmenopausal females only)	X												
Anti-AMG 133-antibody[k,m]			X[d]		X[d]		X[d]		X[d]		X		X
STUDY-SPECIFIC ASSESSMENTS (eg, DISEASE-SPECIFIC ASSESSMENTS, RADIOLOGICAL ASSESSMENTS)													
[redacted]													
PHARMACOKINETIC ASSESSMENTS													
Plasma AMG 133 pharmacokinetics[k,m]			X[d]	X[d]	X[d]	X[d]	X[d]	X	X[d]		X		X
PHARMACODYNAMIC ASSESSMENTS													
[redacted]													
PHARMACOGENETIC ASSESSMENTS													
Pharmacogenetic studies[o,m]		X											
IMAGING													
[redacted]													

BP = blood pressure; C = clinic visit; C-SSRS = Columbia Suicide Severity Rating Scale; cm = centimeters; [redacted]; [redacted] ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; [redacted] FSH = follicle stimulating hormone; [redacted] HIV = human immunodeficiency virus; HR = heart rate; HS-CRP = high-sensitivity C-reactive protein; [redacted] P = phone visit; PD = pharmacodynamic; PHQ9 = Patient Health Questionnaire-9; RR = respiratory rate; [redacted]; SFU = safety follow-up; Temp = temperature.

Please note: Subjects are eligible for an optional in-house residence period on Day 1, 8, 15, and 22 for an overnight observation period. Subjects are eligible for a required in-house residency period for Day 29 and 57. Subjects will receive AMG 133 on Days 1, 8, 15, 22, 29, and 57.

[a] Upon permanent discontinuation from the study treatment for any reason, a SFU visit will be performed approximately 30 (+3) days after the end of the last dosing interval of investigational product.

[b] Eligibility can be confirmed up to -4 days prior to Day 1 to allow for lab tests to result.

[c] Physical exam to include neurologic assessment.

[d] Predose assessment

[e] Single 12-lead ECG

[f] 12-lead ECGs to be performed in a standardized method, in triplicate, and run consecutively (all 3 ECGs should be completed within a total of 5 minutes from start of the first to the completion of the third).

[g] 3 sets of triplicate 12-lead ECGs at baseline (day 1 predose)

[h] Subjects should get vital signs 4 to 5 hours after dosing
[i] Phone call follow up
[j] Analyzed at the local laboratory, additional samples may be collected for safety reasons, at the investigator's discretion.
[k] 10-hour fasting is required at all time points.
[l] Additional on-treatment pregnancy testing may be performed at the investigator's discretion, if there is suspicion that a female subject is pregnant or per local laws and regulations.
[m] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons, at the investigator's discretion.
[n] Local laboratory at screening, then central laboratory at other time points.
[o] For subjects who provided informed consent for the pharmacogenetic studies.

2. Introduction

2.1 Study Rationale

Obesity is a growing global health crisis that is in critical need of safe and effective therapies. Currently approved products provide modest weight loss with side effects that include gastrointestinal intolerability. AMG 133 is a peptide conjugated antibody composed of a human monoclonal antibody (mAb) that binds to and blocks the glucose dependent insulinotropic polypeptide receptor (GIPR) conjugated to 2 identical peptides. The conjugated peptides are glucagon-like peptide 1 (GLP-1) receptor (GLP1R) agonists. 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. The current study evaluates the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD), of single ascending doses (SAD), and multiple ascending doses (MADs) of AMG 133 as a potential therapy for the treatment of obesity.

2.2 Background

2.2.1 Disease

Obesity represents a major threat to public health and the accompanying healthcare costs pose an enormous financial burden (Terranova et al, 2012; Wang et al, 2011). The prevalence of obesity has nearly tripled since 1973 and currently, 650 million adults are obese, defined as having a body mass index (BMI) of ≥30 kg/m^2 (World Health Organization, 2018). Obesity is a major risk factor for type 2 diabetes and cardiovascular disease (CVD) and is associated with increased risk of all-cause and CVD-related mortality (Jensen et al, 2014). Additional comorbidities include nonalcoholic steatohepatitis, polycystic ovary syndrome, obstructive sleep apnea, osteoarthritis, gallbladder and skin diseases, and several forms of cancer (Jensen et al, 2014). In addition, persons with obesity frequently encounter psychological and social problems such as low self-esteem, prejudice, and discrimination (Kolotkin et al, 2001).

Achieving clinically significant weight loss (> 5%) through lifestyle changes focuses on reduced energy intake and increased physical activity, and can improve risk factors for CVD, delay or prevent the development of type 2 diabetes, and contribute to better quality of life (Jensen et al, 2014, Look AHEAD Research Group, 2013). Exercise and nutritional counseling can be effective in the short-term, but many patients will sustain less than 5% weight loss in the long term (Look AHEAD Research Group, 2014).

Currently approved weight loss products belong to the following therapeutic classes: GLP-1R agonists (liraglutide [Saxenda®]), noradrenergic agents (phentermine [Adipex-P®]), lipase inhibitors (orlistat [Xenical®/Alli®]), in addition to fixed combination products (phentermine + topiramate [Qsymia®], and bupropion + naltrexone [Contrave®]). With the currently approved pharmacotherapy for weight management, a modest incremental average weight loss of 2 to 9 kg can be achieved over and above lifestyle measures. Across phase 3 studies of currently approved products, a greater proportion of individuals with obesity on active medication (44% to 75%) achieve a reduction in bodyweight > 5% from baseline over 52 weeks than among those assigned to placebo (23%) (Khera et al, 2016). Side effects of currently approved weight loss products vary depending upon their mechanism and include increased blood pressure, tachycardia, restlessness (stimulants like phentermine), flatulence, and diarrhea (medicines that affect fat absorption, such as orlistat), nausea, vomiting, constipation, dry mouth, and dizziness (molecules that directly interfere with neurotransmitter signaling in the brain, such as bupropion and naltrexone)
(Heymsfield and Wadden, 2017). The majority of persons with obesity are generally dissatisfied with weight loss of less than 10 kg, and as a consequence may discontinue pharmacological treatment to avoid both the costs and side effects accompanying the potential life-long medication (Dalle Grave et al, 2005). Consequently, new pharmacological agents for the treatment of obesity are needed to improve efficacy and reduce side effects.

2.2.2 Amgen Investigational Product Background: AMG 133

The following sections provide an overview of the pharmacology, PK, nonclinical pharmacokinetics, and toxicology of AMG 133. A detailed description of the pharmacology, physical, chemical, and pharmaceutical properties and formulations of AMG 133 is provided in the investigator's brochure.

2.2.2.1 Pharmacology

AMG 133 is a bispecific molecule with functional activities that antagonize GIPR and agonize GLP-1R. AMG 133 is engineered by conjugation of a mAb GIPR antagonist antibody with 2 identical GLP-1 analog peptides, and therefore, exhibits both GIPR antagonism and GLP-1R agonism activities. AMG 133 binds to human GIPR with a dissociation constant (Kd) of 37 pM and inhibits glucose dependent insulinotropic polypeptide (GIP)-induced accumulation of cyclic adenosine monophosphate (cAMP) in human embryonic kidney 293T cells stably expressing human GIPR, with a half-maximal

inhibitory concentration (IC_{50}) of 42.4 nM. In addition, AMG 133 binds to human GLP-1R as demonstrated by the GLP-1 radioligand competition binding assay with an IC_{50} of 55.2 nM. Upon receptor binding, AMG 133 activates GLP-1 and increases cAMP levels in Chinese hamster ovary (CHO) K1 (CHO-K1) cells stably expressing human GLP-1R with half-maximal effective concentration (EC_{50}) of 24.4 pM.

Glucose dependent insulinotropic polypeptide and GLP-1 are gut-derived incretin hormones, well known for their ability to augment glucose stimulated insulin secretion. In addition to the incretin effects, GLP-1 is recognized to promote satiety through the GLP-1R (Turton et al, 1996), and therefore has become an attractive approach to treat patients with type 2 diabetes and obesity (Drucker, 2006). Glucose dependent insulinotropic polypeptide has been shown to promote adiposity (Yip et al, 1998; Beck and Max, 1987; Hauner et al, 1988; Knapper et al, 1995). The GIPR is also recognized to contribute to adiposity as revealed from human and mouse genetic studies, in which genome-wide association studies identified the *GIPR* locus to contribute to measures of body weight (eg, BMI) (Berndt et al, 2013; Okada et al, 2012; Saxena et al, 2010; Speliotes et al, 2010; Wen et al, 2012). In addition, *Gip* and *Gipr* knockout mice are protected from diet-induced obesity (Althage et al, 2008; Miyawaki et al, 2002; Nasteska et al, 2014). Consistent with these data, pharmacological inhibition using anti-GIPR antibodies protected against body weight gain in diet-induced obese (DIO) mice and obese cynomolgus monkeys (Killion et al, 2018). In addition, GIPR antagonism synergistically reduced body weight in combination with GLP-1R agonism in preclinical models (Killion et al, 2018), offering the potential for a bispecific molecule with activities of both GIPR antagonism and GLP-1R agonism for the treatment of obesity.

AMG 133 binds with similar affinity to human, cynomolgus monkey, and mouse GIPR (Kd of 37, 52, and 27 pM, respectively). Whereas AMG 133 functionally inhibits GIP signaling through human and cynomolgus monkey GIPR with similar potency (IC_{50} of 42.4 and 26.5 nM, respectively), it has more than 20-fold lower potency for inhibition of GIP signaling through rat and mouse GIPR. Therefore, an antimouse GIPR surrogate antibody was used to conjugate the same GLP-1 analog peptide used for AMG 133 to generate a mouse surrogate molecule (1238) for pharmacology studies in mice. AMG 133 is a potent agonist on human, cynomolgus monkey, and mouse GLP-1R (EC_{50} of 24.4, 5.7 and 123 pM, respectively).

A murine surrogate,1238, with high potency for both murine GIPR and GLP-1R has been generated for use in mouse preclinical studies. 1238 fully blocks GIP-stimulated cAMP production in CHO AM-1D cells expressing mouse GIPR with an IC_{50} of 4.1 nM and stimulates cAMP production in CHO-K1 cells expressing mouse GLP-1R with an EC_{50} of 90.6 pM.

In PD studies in leptin receptor-deficient (db/db) mice, a single injection of 1238 showed a rapid and sustained effect on lowering blood glucose levels and body weight. In a chronic study, administration of 1238 reduced body weight and food intake in DIO mice. In addition, significant reductions were observed in blood glucose and plasma insulin, cholesterol, triglycerides, aspartate aminotransferase, and alanine aminotransferase levels in mice treated with 1238 compared with the vehicle-treated group.

The efficacy of AMG 133 was evaluated in lean mice and a spontaneously obese cynomolgus monkey model. In lean mice, a single injection of AMG 133 prevented blood glucose elevation during a glucose tolerance test. AMG 133 was evaluated in an obese cynomolgus monkey model using a weekly dosing regimen. In this study, AMG 133 administration reduced body weight, food intake, cholesterol, insulin, and triglyceride levels after 6 weeks of dosing. The weight loss effect was sustained during the dosing free washout period. Taken together, these data suggest that AMG 133 offers the potential to treat obesity in patients.

2.2.2.2 Pharmacokinetics

2.2.2.2.1 Nonclinical Pharmacokinetics

AMG 133 pharmacokinetics is defined depending whether the intact (anti-GIPR monoclonal antibody [mAb] with at least 1 GLP-1 analog peptide) or total (anti-GIPR monoclonal antibodies with or without GLP-1 analog peptides) molecules are detected. AMG 133 exposure after repeat-dose administration over a dose range from 25 to 150 mg/kg in the mouse and 20 to 120 mg/kg in the cynomolgus monkey increased approximately dose proportionally. Exposure ratios of intact to total AMG 133 ranged from 0.81 to 0.85 on day 1 and 0.61 to 0.65 on day 85 in the mouse. In the cynomolgus monkey the exposure ratio of intact to total AMG 133 ranged from 0.87 to 0.92 on day 1, 0.69 to 0.77 on day 43, and 0.66 to 0.72 on day 85. This indicates some clipping of the GLP-1 moiety, but significant exposures to intact AMG 133 were maintained throughout the study. Exposures were similar between male and female animals in both species. In the chronic efficacy study in the cynomolgus monkey, trough plasma concentrations of both the intact and total forms of AMG 133 increased approximately dose proportionally

and were also increased after repeated dosing. The terminal phase plasma concentration-time data implied reasonable stability of the intact form.

For preliminary PK in humans see Section 4.3.

2.2.2.3 Toxicology

Consistent with the International Council for Harmonisation (ICH) S6 (R1) guidance (ICH, 2011), the studies conducted in the nonclinical safety assessment of AMG 133 included in vitro genotoxicity studies, a tissue cross-reactivity study, and exploratory 4-week subcutaneous (SC) repeat-dose and pivotal Good Laboratory Practices-compliant 13-week SC repeat-dose toxicology studies conducted in the mouse and the cynomolgus monkey. The GLP-1 analog peptide portions of AMG 133 contain a non-natural amino acid; the GLP-1 analog peptide was tested for genotoxicity in the bacterial reverse mutation and in vitro human peripheral blood lymphocyte micronucleus tests and did not show any evidence of genotoxic activity in either test. The anti-GIPR mAb in AMG 133 has very high amino acid identity with AMG 598, Amgen's anti-GIPR mAb (IND 135844). Therefore, the results of the tissue cross-reactivity study in a full panel of human tissues with biotin-labeled AMG 598 is considered applicable to AMG 133; no potential AMG 598 cross reactivity in human tissues was identified.

AMG 133 was administered to mice in a 4-week exploratory toxicology study and a 13-week repeat-dose toxicology study. 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. In the 4-week exploratory toxicology study in the mouse, administration of AMG 133 by SC injection once weekly for a total of 4 doses was well tolerated up to 141 mg/kg. The highest tested dose of 658 mg/kg was not tolerated due to severe clinical signs of dehydration. In the pivotal 13-week repeat-dose toxicology study in mice, administration of 25, 75, and 150 mg/kg AMG 133 by SC injection once every 2 weeks for a total of 7 doses was well tolerated, with dose-dependent mild transient clinical observations of suspected dehydration. Exposure to AMG 133 induced anticipated pharmacologically-related changes in mice, including dose-independent body weight loss and, in the pivotal 13-week study, decreases in serum cholesterol and triglyceride levels. There were no AMG 133-related changes in fasting blood glucose or insulin, hematology parameters, macroscopic observations, or light microscopic changes in the pancreas. In the pivotal 13-week study in the mouse, body weight loss was associated with decreased organ weights and light microscopic observations of atrophy of adipose tissue and minimal to mild dilatation of

Brunner's glands in the submucosa of the proximal duodenum. Light microscopic observations of minimal to mild SC inflammation at the injection site and skin in the mouse were considered to be an anticipated localized response to the SC administration of an exogenous protein and were associated with minimal increases in lymphoid cellularity in axillary lymph node and/or minimal or mild increases in extramedullary hematopoiesis in the spleen. In the pivotal 13-week toxicology study in the mouse, the no observed adverse effect level (NOAEL) was the highest tested dose of 150 mg/kg.

In the 4-week exploratory toxicology study in the monkey, weekly SC administration of 11, 56, and 188 mg/kg AMG 133 was well tolerated, and dose-dependent body weight loss was observed. In the pivotal 13-week toxicology study, once every 2 weeks SC administration of 20, 60, or 120 mg/kg AMG 133 for 13-weeks (7 total doses) induced dose-independent body weight loss, indicating maximum pharmacological activity at all tested doses. In the pivotal 13-week study, there were no AMG 133-related effects on clinical observations, neurologic or ophthalmic examinations, quantitative and qualitative electrocardiography, vital signs, fasting blood glucose or insulin, coagulation and urinalysis parameters, biochemical biomarkers for bone metabolism, or organ weights. Nonadverse minimal to mild decreases in red blood cell parameters (hemoglobin, hematocrit, red blood cell counts) and reticulocyte counts were present in both studies in the monkey. 1 female at 120 mg/kg in the 13-week study also had changes in red blood cell morphology and a minimal increase in total bilirubin, suggestive of an increased red blood cell turnover; this change was considered nonadverse due to the small magnitude and lack of clinical observations or evidence of microscopic changes in the liver or gall bladder. There were no macroscopic or microscopic changes in the monkey directly related to AMG 133, including in the pancreas; light microscopic observations of minimal to mild SC mononuclear cell infiltrates at the injection site were considered an anticipated localized response to the SC administration of an exogenous protein. In the pivotal 13-week toxicology in the cynomolgus monkey, the NOAEL was the highest tested dose of 120 mg/kg.

2.2.2.4 Clinical Experience

As of **data entered by December** 2021, in the ongoing first in human (FIH) SAD trial of AMG 133 in subjects with obesity, **57** subjects have received a single dose of AMG 133 or placebo (cohorts 1 **to** 6 **and cohort 11**). The blinded safety data through day 15 of the **840** mg SC dose cohort supports the dose range to be evaluated in this study. Single ascending doses of AMG 133 have been safe and generally well tolerated.

No significant adverse events or deaths have been reported, and most adverse events reported were mild consisting of nausea, vomiting, and dyspepsia. One subject in cohort 3 (140 mg dose) reported moderate adverse events associated with nausea, **abdominal discomfort**, and dyspepsia.

A total of 39 subjects have been enrolled in the MAD trial and have received 1 to 3 doses of AMG 133 or placebo. Most adverse events reported have been after the first dose of AMG 133 and were reported as mild consisting of headache, nausea, vomiting, and diarrhea. There have been no serious adverse events or deaths reported after single or multiple doses. Twenty-six percent of subjects did not receive the second or third dose of AMG 133 either due to adverse events or lost to follow up.

2.3 Benefit/Risk Assessment

The potential long-term benefits of AMG 133 include anticipated weight loss and improved cardiovascular risk factors associated with weight loss. Potential risks of AMG 133, as anticipated from animal data and the literature, are described below in Section 2.3.2.

2.3.1 Key Benefits

There are no key anticipated benefits from short-term use of AMG 133.

2.3.2 Key Risks

Potential risks of AMG 133, as anticipated by evidence from animal data and the literature, include those commonly associated with biologics, including local (eg, injection site) reactions, systemic (eg, hypersensitivity) reactions and immunogenicity (ie, the development of anti-AMG 133 antibodies). Other potential risks include gastrointestinal tolerability issues and risks commonly associated with targeting obesity pathways.

Key potential risks are detailed below.

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.

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 or intravenous (IV) 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.

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 1 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, pharmacokinetics, and pharmacodynamics during the study.

Injection Site Reactions

Injection site reactions (eg, erythema, itching, hematoma, swelling, bruising, and pain) are common side effects of drugs with SC/IV administration. These reactions can range from mild to severe (including injection site necrosis, which is an uncommon side effect). After SC/IV 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.

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of AMG 133 as single and multiple doses in subjects with obesity	• Subject incidence of treatment-emergent adverse events. • Changes in laboratory safety tests, vital signs, and 12-lead electrocardiograms (ECGs)
Secondary	
• To characterize the pharmacokinetics of AMG 133 as single or multiple doses in subjects with obesity	• AMG 133 pharmacokinetic parameters including, but not limited to, maximum observed drug concentration during a dosing interval (C_{max}), the time of maximum observed concentration (t_{max}), and area under the concentration-time curve (AUC)
• To evaluate the immunogenicity of AMG 133	• Incidence of anti-AMG 133 antibody formation
Exploratory	
[redacted]	

Exploratory

[redacted]

3.1 Hypotheses

- AMG 133 will be safe and well tolerated following single and/or multiple SC dose administrations in subjects with obesity across the dose range evaluated
- AMG 133 PK profile following multiple SC dose administrations will support selection of dose and frequency of administration in future multi-dose trials of AMG 133

4. Study Design

4.1 Overall Design

Part A (cohorts 1 **to** 6 and cohort 11) is a phase 1, randomized, double-blind, placebo-controlled, SAD study in adult subjects with obesity. AMG 133 will be administered SC for cohorts 1 to 5 and cohort 11, and IV for cohort 6. Part A consists of a total of 7 cohorts.

Subjects will be confined at the Clinical Research Unit from check-in (morning of day -2) through the morning of day 8 for cohorts 1 to 5 and cohort 11 and, day 6 for cohort 6.

Approximately 56 subjects will enroll into 1 of 7 cohorts. In each cohort, 8 subjects will be randomized to receive AMG 133 or placebo SC (cohorts 1 to 5 and cohort 11) or IV (cohort 6) in a 3:1 ratio as described in Table 7. For cohort 1, the first 2 subjects (sentinel pair) will be randomized such that 1 subject will receive AMG 133 and 1 subject will receive placebo. The sentinel pair will be observed for at least 48 hours before the remaining subjects in the cohort are dosed, provided there are no safety or tolerability concerns as assessed by the investigator. Enrollment into the SAD cohorts will be sequential. Subsequent cohorts will be dosed after the dosing regimen in the preceding cohort has been recommended by the Dose Level Review Team (DLRT) to be safe and

well tolerated based on the safety and laboratory data through at least day 15 for at least 7 out of 8 subjects dosed. Subjects in cohorts 1 to 5 and cohort 11 will also participate in [redacted] tests at day -1 and day 7.

Part B (cohorts 7 **to** 10) is a randomized, placebo-controlled, double-blind, MAD study in adult subjects with obesity. In each cohort, subjects will be randomized to receive AMG 133 or placebo SC in a 3:1 ratio as described in Table 7. Approximately 24 subjects will enroll into cohorts 7 **to** 9. Cohorts 7 **to** 9 will include assessments of [redacted] Enrollment into Part B cohort 7 will occur with a starting MAD dose that is at least 2 SAD dose levels below what was recommended by the DLRT to be safe and reasonably tolerated in Part A. Enrollment into the MAD cohorts 8 and 9 will be sequential.

Subjects in cohorts 8 and 9 will be dosed after the dose regimen in the preceding MAD cohort has been recommended by the DLRT to be safe and reasonably tolerated based on safety and laboratory data through at least study day 36 for 6 out of 8 subjects dosed. The DLRT for SAD cohort 11 will also make dosing recommendations for cohort 9 (Figure 1-1 [A]). [redacted] All subjects in each Part B (MAD) cohort may be dosed on the same day.

Cohort 10 will enroll **up to** 20 subjects and will include the [redacted]. Therefore, the dose recommended for cohort 10 should be the same as a dose studied in a previous cohort.

The dose recommended for cohort 10 will depend on the final dose recommended for cohort 9 and the safety and tolerability profiles for MAD cohorts 7 and 8 (Figure 1-1 [B]).

[redacted]

[redacted]

In all dose escalation process, DRLM will make a recommendation and Amgen will make the final decision on dose level.

- MAD cohorts 7 **to** 9: Study drug will be administered every 4 weeks for a total of 3 SC doses. The dose levels will be defined after evaluation of the available PK and PD data from preceding cohorts in the SAD phase (Part A). Three different dose levels will be evaluated with the lowest dose administered to cohort 7, and 2 higher ascending doses administered to cohorts 8 and 9. The dose level for cohorts 7 **to** 9 will not exceed the highest dose evaluated in cohorts 1 **to** 6 and cohort 11 (Part A). Subjects enrolled in cohorts 7 **to** 9 will also be asked to [redacted]
- MAD cohort 10: **Up to t**wenty subjects will be randomized in a 3:1 ratio to receive AMG 133 or placebo SC. All subjects will be asked to use [redacted] The dose level will not exceed the highest dose evaluated in cohorts 7 **to** 9 (Part B).

Part C (cohorts 12 to 13) is an open-label modified dose-escalation MAD study in subjects with obesity. Approximately 12 subjects (up to 6 subjects per cohort) will enroll in Part C and receive AMG 133 (see Table 7). Doses selected for these cohorts are known to have an acceptable safety and tolerability profile based on data reviewed by the DLRT from previous cohorts in Part A and Part B and will not exceed the dose levels previously studied in the MAD cohorts 7 to 9. Cohort 12 will receive [redacted] mg SC on days [redacted] followed by [redacted] mg SC on days [redacted] Cohort 13 will receive [redacted] mg on days [redacted] followed by [redacted] mg SC on days [redacted]. Cohorts 12 and 13 will enroll in parallel. The DLRT will review the safety and laboratory data through at least day 36.

Table 7. Planned Dose Levels by Cohort

	Cohort	No. Subjects	AMG 133/Placebo Dose/ Frequency	Route	N (active: placebo)
Part A	1	8	21 mg day 1	SC	6:2
	2	8	Not exceeding 70 mg day 1[a]	SC	6:2
	3	8	Not exceeding 140 mg day 1[a]	SC	6:2
	4	8	Not exceeding 280 mg day 1[a]	SC	6:2
	5	8	Not exceeding 560 mg day 1[a]	SC	6:2
	11	8	Not exceeding 840 mg day 1[a]	SC	6:2
	6	8	Not exceeding 70 mg day 1[a]	IV	6:2
Part B	7	8	Not exceeding 140 mg[b] Q4W x 3	SC	6:2
	8	8	Not exceeding 280 mg[b] Q4W x 3	SC	6:2
	9	8	Not exceeding 560 mg[b] Q4W x 3	SC	6:2
	10	≤ 20	Not exceeding 560 mg[c] Q4W x 3 + [redacted]	SC	≤ 15:5
Part C	**12**	**≤ 6**	[redacted]	**SC**	**N/A**
	13	**≤ 6**	[redacted]	**SC**	**N/A**

N/A = not applicable; Q4W = every four weeks; SC = subcutaneous; IV = intravenous.
[a] Actual dose levels will be based on available data from previous cohorts.
[b] Dose will not exceed the highest dose evaluated in cohorts 1 to 5 and cohort 11 (Part A)
[c] Dose will not exceed the highest dose evaluated in cohorts 7 **to** 9 (Part B)

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

4.2 Number of Subjects

A total of approximately **112** subjects will be enrolled in the study. Approximately 56 subjects will be enrolled in Part A of the study, with 8 subjects in each of the 7 cohorts. Approximately 44 subjects will be enrolled in Part B of the study, with 8 subjects in cohorts 7 **to** 9 and **up to** 20 subjects in cohort 10. **Up to 12 subjects will be enrolled in Part C cohorts 12 to 13.** Additional subjects may be enrolled if a DLRT recommendation is made to expand, repeat, or add cohorts to the study **or if replacement subjects are needed**.

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

4.2.1 Replacement of Subjects

Subjects who withdraw from the study or who discontinue study drug administration prematurely may be replaced at the discretion of Amgen in consultation with the investigator. The replacement subject will be assigned to receive the identical treatment as the replaced subject.

4.2.2 Number of Sites

Approximately 1 to **3** investigative sites in United States will be included in the study. Sites that do not enroll subjects within 1 month of site initiation may be closed.

4.3 Justification for Investigational Product Dose

The planned cohort in this amendment of the study consists of a multiple-dose cohort following a titration schema as presented in Figure 1-1.

Previously, subjects in Part A **received single doses of AMG 133** - 21, 70, 140, 280, 560, and 840 mg administered SC. This part also consist**ed** of an IV cohort (cohort 6) at a dose of 70 mg administered IV; **all SAD** have been completed. The starting dose and exposure multiples for the doses evaluated in SAD were calculated based on the NOAELs determined in the 13-week Good Laboratory Practices repeat-dose mouse and cynomolgus monkey nonhuman primate toxicology studies (every 2 weeks dosing, Section 2.2.2.3) and the observed reduction in body weight in the chronic efficacy study in obese cynomolgus monkeys.

Part B consist**ed** of evaluation of AMG 133 **following repeat doses - 140, 280, and 420 mg administered Q4W for a total of 3 doses per cohort.** Preliminary review of the PK data in the FIH SAD **and MAD** part of the study demonstrated that AMG 133 pharmacokinetics follow a linear, dose proportional kinetics based on C_{max} (area under the curve [AUC] data pending), with a half-life of approximately 15 **to 20** days.

For **SAD** cohorts 1 **to** 6 **and 11**, no **serious adverse events** or deaths have been reported, and most **adverse events** reported were mild associated with nausea, vomiting**, and dyspepsia**. One subject in cohort 3 (140 mg dose) had a moderate adverse event associated with gastroenteritis **related to IP. Approximately 90% of subjects enrolled in MAD cohorts 7 to 10 reported mild GI-related adverse events (mainly nausea, vomiting, and diarrhea) after the first dose of AMG 133 and less than 5% experienced GI-related adverse events after the second dose. There were no serious adverse events or deaths reported after any of the doses. Approximately 26% of subjects in the MAD trial discontinued the study prior to**

receiving the second dose which caused concerns regarding tolerability of the first dose; 50% of subjects in cohort 9 withdrew consent after receiving the 420 mg dose on day 1 due to GI-related adverse events. The doses were selected to allow for whole integer injection volumes to circumvent any potential dosing errors.

Part C consists of two cohorts (cohorts 12 and 13), both open-label to evaluate dose-level escalation from 70 mg to 420 mg. The objective of Part C is to evaluate first dose effects of AMG 133 on GI-related adverse events using a titration methodology. Cohort 12 will start at a lower dose [redacted] mg) of AMG 133 given [redacted].

Cohort 13 will start at a lower dose ([redacted] mg) of AMG 133 given [redacted].

The rationale for dose selection for Part C is based on the available PK data from this ongoing FIH study cohorts 1 to 11 (Part A and Part B) and the NOAEL exposures established based on 13-week GLP repeat-dose studies in mouse and cynomolgus monkeys.

Similarly, for cohort 12, the predicted human exposure multiples for intact AMG 133 following the second dose of [redacted] mg on Day [redacted] are approximately 40.5-fold and 45-fold for C_{max} and AUC_{ss}, respectively, based on NOAEL established in cynomolgus monkeys, and 43-fold and 42.4-fold for C_{max} and AUC_{ss}, respectively, based on NOAEL established in mice. The predicted human exposure multiples for total AMG 133 following the second dose of [redacted] mg on Day [redacted] are approximately 45-fold and 49-fold for C_{max} and AUC_{ss}, respectively, based on NOAEL established in cynomolgus monkeys, and 54-fold and 42-fold for C_{max} and AUC_{ss}, respectively, based on NOAEL established in mice (Table 8 and Table 9).

For cohort 13, the predicted human exposure multiples for intact AMG 133 following the second dose of [redacted] mg on Day [redacted] are approximately 39-fold and 43.2-fold for C_{max} and AUC_{ss}, respectively, based on NOAEL established in cynomolgus monkeys, and 41.3-fold and 40.6-fold for C_{max} and AUC_{ss}, respectively, based on NOAEL established in mice. The predicted human exposure multiples for total AMG 133 following the second dose of [redacted] mg on

Day [redacted] are approximately 42.2-fold and 45.5-fold for C_{max} and AUC_{ss}, respectively, based on NOAEL established in cynomolgus monkeys, and 50.9-fold and 47.5-fold for C_{max} and AUC_{ss}, respectively, based on NOAEL established in mice (Table 8 and Table 9).

Table 8. Estimated Exposure Margins of Intact AMG 133 Following Repeat Doses (Q4W)

Clinical Dose (mg)	Route	Predicted Human Exposure		Predicted Exposure Multiples[a]			
				Mouse[b]		Monkey[c]	
		AUC_{0-28} (μg·hr/mL)	C_{max} (μg/mL)	AUC[d]	C_{max}[e]	AUC[d]	C_{max}[e]
[redacted] (cohort 12)[f]	SC	**17 731**	**37**	**42.4**	**43**	**45.1**	**40.5**
[redacted] (cohort 13)[f]	SC	**18 513.6**	**38.5**	**40.6**	**41.3**	**43.2**	**39**

AUC = area under the concentration-time curve; AUC_{last} = area under the concentration-time curve during a last dosing interval; AUC_{0-28} = area under the concentration-time curve during a dosing interval defined here from time **0 to 28 days** after **the 2nd dose**; C_{max} = maximum observed drug concentration during a dosing interval defined here after the **2nd** dose; FIH = First in Human; NOAEL = no observed adverse effect level; PK = pharmacokinetic; SC = subcutaneous; Q4W = every 4 weeks.

[a] PK data from AMG 133 FIH study is used for PK prediction

[b] After the last dose after 13 weeks of treatment (7 total doses) at the NOAEL dose of 150 mg/kg in mice (Study 150238); mean AUC_{last} **($AUC_{0-168hrs}$)** of 188 000 μg·hr/mL and mean C_{max} of 1590 mg/mL of Intact AMG 133.

[c] After the last dose after 13 weeks of treatment (7 total doses) at the NOAEL dose of 120 mg/kg in cynomolgus monkeys (Study 150239); mean AUC_{last} **($AUC_{0-168hrs}$)** was 200 000 μg·hr/mL and mean C_{max} of 1500 mg/mL of Intact AMG 133.

[d] AUC exposure multiples = ratio of AUC_{last} after 13 weeks (7 doses) of AMG 133 administration in the mouse or monkey x 4/predicted **AUC_{0-28}** in humans after the **2nd** dose.

[e] C_{max} multiple = the ratio of C_{max} after the last dose after 13 weeks (7 doses) of AMG 133 in the mouse or monkey to the predicted C_{max} for each human single dose.

[f] Actual dose levels will be based on available data from previous cohorts.

Source: Report 153788

Table 9. Estimated Exposure Margins of Total AMG 133 Following Repeat Doses (Q4W)

Clinical Dose (mg)	Route	Predicted Human Exposure		Predicted Exposure Multiples[a]			
				Mouse[b]		Monkey[c]	
		AUC_{tau} (μg·hr/mL)	C_{max} (μg/mL)	AUC[d]	C_{max}[e]	AUC[d]	C_{max}[e]
[redacted] (cohort 12)[f]	SC	**22 831**	**43.5**	**51**	**54.3**	**48.9**	**45.1**
[redacted] (cohort 13)[f]	SC	**24 504**	**46.4**	**47.5**	**50.9**	**45.5**	**42.2**

AUC = area under the concentration-time curve; AUC_{0-28} = area under the concentration-time curve during **a** dosing interval defined here from time **0 to 28 days** after **the 2nd dose**; C_{max} = maximum observed drug concentration during a dosing interval defined here after the **2nd** dose; FIH = First in Human; NOAEL = no observed adverse effect level; PK = pharmacokinetic; SC = subcutaneous; Q4W = every 4 weeks.

[a] PK data from AMG 133 FIH study is used for PK prediction

[b] After the last dose after 13 weeks of treatment (7 total doses) at the NOAEL dose of 150 mg/kg in mice (Study 150238); mean AUC_{last} **($AUC_{0\text{-}168hrs}$)** of 291 000 μg hr/mL and mean C_{max} of 2360 mg/mL of Total AMG 133.
[c] After the last dose after 13 weeks of treatment (7 total doses) at the NOAEL dose of 120 mg/kg in cynomolgus monkeys (Study 150239); mean AUC_{last} **($AUC_{0\text{-}168hrs}$)** was 279 000 μg hr/mL and mean C_{max} of 1960 mg/mL of Total AMG 133.
[d] AUC exposure multiples = ratio of AUC_{last} after 13 weeks (7 doses) of AMG 133 administration in the mouse or monkey x 4/predicted **($AUC_{0\text{-}28\ days}$)** in humans after the **2nd** dose.
[e] C_{max} multiple = the ratio of C_{max} after the last dose after 13 weeks (7 doses) of AMG 133 in the mouse or monkey to the predicted C_{max} for each human single dose.
[f] Actual dose levels will be based on available data from previous cohorts**.**

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s).

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

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

4.4.2 Study Duration for Subjects

The planned duration of participation in the study is approximately 178 days for Part A**,** 235 days for Part B**, and up to 235 days for Part C**.

4.5 Patient Input on Study Design

Patient input was not obtained in the design of this study.

5. Study Population

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

Eligibility criteria will be evaluated during screening.

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

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

5.1 Inclusion Criteria

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

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

102 Age ≥ 18 years to ≤ 65 years, at the time of signing the informed consent.

103 Except for obesity, otherwise healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and ECGs on day -2 (cohorts 1 **to** 6, cohort 11 **to 13**) or day -1 (cohorts 7 **to**10) and screening.

104 BMI between ≥ 30.0 kg/m^2 and ≤ 40.0 kg/m^2.

105 Have a stable body weight (< 5 kg self-reported change during the previous 8 weeks) before screening.

106 Willing to maintain current general diet and physical activity regimen, except for the physical activity in the 72 hours before each blood sample collection for the clinical laboratory analysis, which should not be strenuous.

107 Females must be of nonreproductive potential

- Postmenopausal as defined as:
  - Age of ≥ 55 years with no menses for at least 12 months; OR
  - Age < 55 years with no menses for at least 12 months AND with a follicle-stimulating hormone level > 40 IU/L or according to the definition of “postmenopausal range” for the laboratory involved; OR
- History of hysterectomy; OR
- History of bilateral oophorectomy.

108 For patients in cohorts 7 **to** 10 only, subjects must have a smartphone device with the capability of downloading apps or other digital tools required for this cohort.

5.2 Exclusion Criteria

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

Other Medical Conditions

201 History or clinical evidence of diabetes mellitus, including HbA1c > 6.5% and/or a fasting glucose ≥ 125 mg/dl (6.9 mmol/L) at screening.

202 Triglycerides ≥ 5.65 mmol/L (ie, 500 mg/dL) at screening.

203 Screening calcitonin ≥ 50 ng/L.

204 Hepatic liver enzymes aspartate aminotransferase **(AST)**, alanine aminotransferase **(ALT)**, alkaline phosphatase, or total bilirubin levels > 1.5 times the upper limit of normal (ULN) at screening. **If ALT is > 1.5 x the ULN at screening AND the AST, alkaline phosphatase, and total bilirubin levels are within normal limits, then subject may be eligible for enrollment after a discussion with the medical monitor.**

205 History or clinical evidence of bleeding diathesis or any coagulation disorder, including prothrombin time **(PT)**, activated partial thromboplastin time **(PTT)**, international normalized ratio **(INR)**, or platelet count outside of the laboratory's normal reference range at screening. **If a single value (PT, PTT, INR, or platelet count) is outside the normal reference range at screening and the subject does not have evidence of any other bleeding or coagulation disorder, then the subject may be eligible for enrollment after a discussion with the medical monitor.**

206 History of gastrointestinal abnormality that could affect gastrointestinal motility (including small bowel or colonic resection, inflammatory bowel disease, irritable bowel disease, and colon or gastrointestinal tract cancer).

207 Subjects with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 or a personal history of nonfamilial medullary thyroid carcinoma.

208 Subjects with a history of confirmed chronic pancreatitis or idiopathic acute pancreatitis.

209 Subjects with a history of gall bladder disease (ie, cholelithiasis or cholecystitis) not treated with cholecystectomy.

210 Untreated or uncontrolled hypothyroidism/hyperthyroidism defined as thyroid-stimulating hormone > 6 mIU/L or < 0.4 mIU/L.

211 A corrected QT interval (QTc) at screening of > 450 msec in males or > 470 msec in females or history of long QT syndrome.

212 Subjects with a history of renal impairment or renal disease and/or estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2.

213 Obesity induced by other endocrinologic disorders (eg, Cushing's Syndrome).

214 Previous surgical treatment for obesity (excluding liposuction if performed >1 year before study entry) and/or subjects with recent (within 6 months) or planned endoscopic treatment for obesity.

215 History of major depressive disorder.

216 History of other severe psychiatric disorders, eg schizophrenia, bipolar disorder.

217 Any lifetime history of a suicidal attempt or of any suicidal behavior.

218 Surgery scheduled for the study duration period, except for minor surgical procedures, at the discretion of the investigator.

219 Positive results for human immunodeficiency virus antibodies, hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C virus RNA. For hepatitis C, hepatitis C antibody testing is done at screening, followed by hepatitis C virus RNA by polymerase chain reaction if hepatitis C antibody is positive.

220 Systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 90 mm Hg at screening, or on day -2. For each visit, if the initial blood pressure is elevated, the reading may be repeated once at least 15 minutes later and the lower of the 2 readings may be used.

221 History of malignancy of any type, other than in situ cervical cancer or surgically excised nonmelanomatous skin cancers occurring more than 5 years before randomization.

Prior/Concomitant Therapy

222 Use of the following agents are excluded unless there is a prior consultation between the investigator and Amgen medical monitor:

- Prescription and nonprescription drugs within 14 days or 5 half-lives, whichever is longer, before the first dose of investigational product, with exception of hormone replacement therapy (eg, estrogen, thyroid).
- All herbal medicines, vitamins, and supplements within 30 days before receiving the first dose of investigational product.
- Exceptions must be reviewed and approved by the investigator and Amgen medical monitor. Written documentation of this review and Amgen acknowledgment is required for subject participation.

223 Current or history of treatment with medications that may cause significant weight gain or loss, within 3 months before screening, including systemic corticosteroids (except for a short course of treatment, ie, 7 to 10 days), tricyclic antidepressants, atypical antipsychotic and mood stabilizers (eg, imipramine, amitriptyline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium).

224 Current participation (or within the last 3 months) in an organized weight reduction program or currently using or used within 3 months before screening: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phentermine, naltrexone, bupropion, lorcaserin, metformin, or any GLP-1R agonists (either by prescription or as part of a clinical study).

Prior/Concurrent Clinical Study Experience

225 Prior exposure to AMG 133 or AMG 598 or currently receiving treatment in another investigational device or drug study, or less than 5 half-lives since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

226 Female subjects with a positive pregnancy test assessed at screening and/or day -2 by a serum pregnancy test and/or urine pregnancy test) or female subjects who are breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 5 months after the last dose of AMG 133.

227 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use an acceptable method of contraception during treatment and for an additional 5 months after the last dose of AMG 133. Refer to Section 11.5 for additional contraceptive information.

228 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 5 months after the last dose of AMG 133.

230 Subject has a known sensitivity to GLP-1R agonists.

231 Subject has known sensitivity to mammalian derived products.

232 Subject has an allergy or known sensitivity to acetaminophen.

233 Subject is unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol is prohibited 48 hours before day -2 and is limited to no

more than to 2 drinks per day for males and 1 drink per day for females for the duration of the study (1 drink being equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits).

234 Subject uses nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, e-cigarettes, pipes, or nicotine patches) within 6 months before screening. Subject is unwilling or unable to abstain from nicotine or tobacco, cigars, cigarettes, pipes, or nicotine patches throughout the course of the study.

235 Subject is tested positive for alcohol and/or drugs of abuse at screening.

236 History of substance abuse (ie, alcohol, licit or illicit drugs) within 12 months before screening.

237 Subject is unwilling to refrain from strenuous exercise (eg, heavy lifting, weight training, and aerobics) for 72 hours before each blood collection for clinical laboratory tests.

238 Subject has donated or lost ≥ 500 mL of blood or plasma within 60 days of day -2.

239 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

240 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

241 For subjects in cohorts 7 **to** 10 **and cohorts 12 to 13** only, the Patient Health Questionnaire-9 (PHQ-9) score of ≥ 10 up to day 1

242 For subjects in cohorts 7 **to** 10 **and cohorts 12 to 13** only, any suicidal ideation as identified by endorsement of (answered yes to) any of the items numbered 1 to 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) up to day 1

243 For subjects in cohorts 7 **to 10 and cohorts 12 to 13** only, **s**ubject has systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 95 mm Hg on day 1. For each visit, if the initial blood pressure is elevated, the reading may be repeated once at least 15 minutes later and the lower of the 2 readings may be used

244 For subjects in cohorts 7 **to 10 and cohorts 12 to 13** only, a QTc of > 450 msec in males or > 470 msec in females up to day 1

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Subjects will be required to fast overnight for at least 10 hours before all blood draws for routine clinical laboratory [redacted] plasma pharmacokinetics, and pharmacodynamics assessments [redacted] per Schedule of Activities

(Section 1.3). After dosing, no water is allowed for 2 hours, after which water is allowed ad libitum.

5.3.2 Caffeine, Alcohol, and Tobacco

Subjects must limit alcohol consumption throughout the course of the study. Alcohol is prohibited 48 hours before admission to the research facility on day -2. For all subjects, alcohol consumption is limited to no more than 2 drinks per day for males, 1 drink per day for females, for the duration of the study (1 drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits).

Only non-nicotine or nontobacco using subjects should be enrolled. Subjects should not have used any nicotine or tobacco containing products within the last 6 months before screening. Subjects must abstain from nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, e-cigarettes, pipes, or nicotine patches) throughout the screening period and for the duration of the study.

5.3.3 Activity

Subjects will abstain from strenuous exercise for 72 hours before each blood sample collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (eg, watching television, reading).

5.4 Subject Enrollment

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

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

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (after signing the consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned

through IRT. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

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

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, 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. Refer to Section 8.1.1.

5.6 Washout Period/Run-in Period/Invasive Procedures

There will be no washout period, run-in period, or invasive procedures in this study.

6. Treatments

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

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 10 below.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 10. Study Treatments

Study Treatment Name	**Amgen Investigational Product:**[a] AMG 133	**Placebo**
Dosage Formulation	[redacted]	Placebo will be presented in identical containers, and stored/packaged the same as AMG 133.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	cohorts 1 to 5: 21 mg SC, or a dose based on available data from previous cohorts, not exceeding 70, 140, 280, or 560 mg SC cohort 6: Dose based on available data from previous cohorts, not exceeding 70 mg IV cohorts 7 **to** 9: a dose based on available data from previous cohorts, not exceeding 140, 280, or 560 mg SC cohort 10: Dose based on available data from cohorts 7, 8, or 9, not exceeding 560 mg SC. cohort 11: Dose based on available data from cohorts 1 to 5, not exceeding 840 mg SC. **cohorts 12 to 13: Dose based on available data from cohorts 1 to 11,** [redacted]	NA
Route of Administration	IV/SC injection	
Accountability	The unblinded pharmacist must provide AMG 133 or placebo from the Amgen supplied stock according to the IRT assignment. The volume of preparation, dose, start date/time, and lot number (after study is unblinded) of AMG 133 is to be recorded on each subject's CRF(s).	

Study Treatment Name	**Amgen Investigational Product:**[a] AMG 133	**Placebo**
Dosing Instructions	Administration of AMG 133 or placebo requires specific training, which must be completed and documented before undertaking any administration related activities. AMG 133 will be delivered as 1+ injections SC or IV. cohorts 1 to 5 and cohorts 7 to 13: AMG 133 or placebo should be administered in the abdominal subcutaneous tissue by SC injection. Where more than 1 injection is required to administer the full dose, the subject will receive the SC injections in different quadrants in the abdominal SC tissue 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 2 mL of AMG 133 or placebo in the order described above. cohort 6: AMG 133 or placebo should be administered by a short duration bolus injection over 3 to 5 minutes in accordance with local policy. Additional dosing instructions are provided in the IPIM.	

CRF = case report form; IPIM = Investigational Product Instruction Manual; IRT = interactive response technology; IV = intravenous; NA = not applicable; SC = subcutaneous

[a] AMG 133 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Noninvestigational Products

No Amgen noninvestigational products will be used in this study.

6.1.3 Medical Devices

No Amgen investigational medical devices will be used in this study.

Investigational medical devices are not used in this study. However, non-investigational devices such as **an iPhone may be used with cohorts 7 to 9 and** a [redacted] Amgen will be responsible for providing the devices to the investigators for use by subjects.

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

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

Additional details are provided in the IPIM.

6.1.4 Other Protocol-required Therapies

All other protocol-required therapies including, [redacted], that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Subjects participating in cohorts 1 to 5 and cohort 11 will undergo a [redacted] test after an overnight fast of a minimum of 10 hours. [redacted] are summarized in the Schedule of Activities in **Section 1.3**. [redacted] tests will not be performed in cohorts 6 **to** 10 **and cohort 12 to 13**.

6.1.5 Other Treatment Procedures

There will be no other treatment procedures in this study.

6.1.6 Product Complaints

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

This includes any investigational**/non-investigational** product**(**s**), device(s) or combination product(s)** provisioned and/or repackaged/modified by Amgen**:**

AMG 133

Any product complaint(s) associated with **an** investigational product**(**s**), non-investigational products(s), devices(s), or combination product(s)** supplied by Amgen are to be reported.

As an industry-wide standard practice, the study site staff (whether experienced it him/herself or experienced/reported by a study participant) is advised to communicate an adverse event and/or a product complaint associated * with the non-Amgen wearable device to the legal manufacturer of that device as soon as possible.

*Note: By association means that an adverse event demonstrates temporal and/or spatial associations with the non-Amgen wearable device. Please refrain from including further adjudication of such events in the communications to the device manufacturer and the expectedness of the event by investigators and by Amgen safety medical reviewers.

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

With the exception of hormone replacement therapy (eg, estrogen, thyroid), use of any prescription or nonprescription drugs within the 14 days or 5 half-lives (whichever is longer) before the first dose of investigational product on day 1, and for the duration of the study, is not permitted unless to treat a medical emergency. In addition, use of herbal medicines, vitamins and supplements within 30 days before dosing on day 1, and for the duration of the study, is not permitted unless reviewed and approved by the investigator and Amgen medical monitor. Any changes regarding concomitant medications should be recorded on the subject's source documents and the CRF along

with the reason for the change. Use of any medication that may cause significant weight gain or loss, including systemic corticosteroids (except for a short course of treatment, ie, 7 to 10 days), tricyclic antidepressants, atypical antipsychotic, and mood stabilizers (eg, imipramine, amitriptyline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium) within 3 months before screening, and for the duration of the study is not permitted.

6.2 Dose Modification

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

Dose Level Determination

A recommendation to escalate to a higher dose cohort will only occur when the previous dose regimen(s) have been found to be reasonably well tolerated based on available study data through study day 15 for a minimum of 7 out of 8 dosed subjects (cohorts 1 **to** 6 and cohort 11) or through study day 36 for 6 of 8 dosed subjects (cohorts 7 **to** 10) and upon unanimous agreement of the DLRT members. Available data from previous cohorts will also be considered. Dose level recommendations will be made on a treatment cohort basis (not on an individual basis). After receiving the DLRT recommendation, Amgen will render a final decision and will issue a written notification of the dose change decision to investigators. **The DLRT will not make a dose level recommendation after reviewing the safety and tolerability data through study day 36 for subjects in cohorts 12 to 13 as these are terminal cohorts.** Further information on DLRMs is provided in Appendix 3 (Section 11.3).

Dose Cohort Stopping Rules

The DLRT will recommend stopping or modifying dosing if suspected adverse drug reactions, changes in vital signs, ECG, or clinical laboratory results are observed and these changes pose a significant health risk. In addition, dosing will be stopped or modified if any of the stopping rules shown in Table 11 are met. The Amgen medical monitor may suspend dosing and convene a DLRM at any time based on emerging safety data.

Dosing will be stopped or modified as shown in Table 11.

Table 11. Dose Cohort Stopping Rules

Scenario	Action
Any occurrence of an Amgen Standard Grading Scale moderate adverse event of similar type in 2 or more subjects in the same cohort.	Stop dosing and convene DLRM (if event occurs outside the regularly scheduled DLRM). Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding, as appropriate.[a] Based on the DLRM vote, 1 of the following recommendations may be made: • stop enrollment of the cohort (if applicable) • resume enrollment of the cohort as planned • expand the cohort at the same dose • continue enrollment of the study at a lower dose • upon a unanimous vote escalate to an intermediate dose (a dose lower than the next planned dose) • upon a unanimous vote escalate to the next planned dose
Any occurrence of an Amgen Standard Grading Scale severe adverse event.	Stop dosing additional subjects in the cohort and convene DLRM (if the event occurs outside the regularly scheduled DLRM). Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding to determine relatedness to investigational product.[a] If the adverse event is determined by a majority vote of the DLRT to be related to study drug and clinically or medically significant, recommend that no further doses should be administered at this dose and no dose escalation should proceed. Recommend that enrollment of the study continue at a lower dose or a lower dose cohort may be added to the study. Otherwise, based on the majority vote of the DLRT, 1 of the following recommendations may be made: • resume enrollment of the cohort as planned • expand the cohort at the same dose • continue enrollment of the study at a lower dose or add a lower dose cohort to the study.

DLRM = dose level review meeting; DLRT = dose level review team

[a] A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject or may impact the safety of subjects currently enrolled or of subjects in subsequent cohorts.

Clinically or medically significant serious adverse events and suspected adverse drug reactions considered to be related to study procedures will be followed until resolved or considered stable.

The study may be terminated at any point at the discretion of the sponsor.

Individual Stopping Rules

No individual dose stopping rules will be implemented.

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

6.2.2.1 Amgen Investigational Product: AMG 133

The reason for dose change of AMG 133/placebo is to be recorded on each subject's CRF(s).

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

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

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and other protocol-required therapies during the study are provided in the IPIM.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects will be randomized in a 3:1 allocation ratio, to AMG 133 to placebo, respectively, in double-blind manner **in Part A and Part B cohorts 1 to 11 only. Part C cohorts 12 to 13 is an open-label study**.

The randomization will be performed by IRT.

Subjects will be assigned a randomization number based in sequential order in which they qualified to be randomized. Subjects will be considered randomized once a unique subject randomization number has been assigned.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

6.4.2 Blinding

This is a double-blind study **for cohorts 1 to 11**. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

6.4.2.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for

any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.4.2.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Amgen staff and their designees involved in the study will not be blinded but will only be given treatment assignments when there is a need to use the information for analysis, discussion, and internal decision making. Access to treatment assignments and other restricted data are described in Amgen standard documents. Unblinded individuals are to ensure unblinding and potentially unblinding information should not be distributed to the investigators or subjects before the study is formally unblinded.

6.5 Treatment Compliance

Investigational product will be administered at the clinic by qualified staff.

6.6 Treatment of Overdose

The effects of overdose of AMG 133 are not known. In case of dosing error, immediate consultation with the Amgen medical monitor is recommended to discuss subject management and prompt reporting of clinically apparent or laboratory adverse events possibly related to the dosing error.

In case of overdose, subjects should be closely monitored for signs and symptoms of adverse events. Pharmacokinetic assessments should be obtained if possible.

Subjects should be monitored closely until any observed signs and/or symptoms revert to normal.

Adverse events should be reported and documented according to instructions available in Section 8.2.3.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior therapies that were being taken/used from 14 days or 5 half-lives before enrollment through the first dose of investigational product will be collected. For all prior therapies, collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.7.

Concomitant therapies are to be collected from enrollment through the end of study. For all concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

7. Discontinuation Criteria

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2.1, and 7.2.2.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see **Section 1.3**) including different options of follow up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 11.3.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Pregnancy

7.2 Discontinuation From the Study

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

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

7.2.1 Reasons for Removal From Washout Period, Run-in Period, or Invasive Procedures

There will be no washout period, run-in period, or invasive procedures during this study.

7.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

7.3 Lost to Follow-up

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

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

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

8. Study Assessments and Procedures

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

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

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

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject to assess eligibility for participation. The screening window is up to 28 days.

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

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1 time after sponsor approval.

If the subject meets eligibility criteria but is not enrolled within the 28-day screening period, a new 28-day screening window may begin for an open cohort and all screening procedures should be repeated. This subject is not registered as a screen fail.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (**Section 1.3**). On-study visits may be completed within the windows provided. The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-required therapies is to be administered after all predose assessments and/or procedures during each visit that it is required.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the end of the last

dosing interval of investigational product. End of Study visit procedures should be performed at this safety follow-up visit per the Schedule of Activities (**Section 1.3**).

8.1.4 End of Study

End of study visit procedures will be performed per the Schedule of Activities (**Section 1.3**). For subject completing the study, this visit occurs on day 150 ± 7 (Part A) and day 207 ± 7 (Part B**), and up to day 207 ± 7 days (Part C)**. If feasible, all end of study procedures should be performed at the final visit for subjects who are removed from study before the defined end of study visit

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

During the study, every effort should be made to perform the study procedures as indicated on the Schedule of Activities (**Section 1.3**). Every effort should be taken to collect all laboratory, biomarker, and pharmacokinetic samples as described in the Schedule of Activities (**Section 1.3**). If sample processing/shipment on a weekend/holiday is not logistically feasible for a site, this needs to be documented and will not be considered a protocol deviation.

Subjects will be seen in the clinic for study evaluations. When ECGs, vital signs, and blood sample collections occur at the same visit, ECGs and vital signs should be collected before blood samples. The time of blood sample collection must be recorded with the exact time of collection (do not use the time that samples were frozen or at any other time point). The study-specific manuals provide additional details regarding the requirements for these procedures.

Acceptable deviation windows applicable to visits, ECG capture, dosing, and sample collections follow:

- ± 5 minutes window around the target completion time for tests and samples through 24 hours postdose (with the exception of the first 10-minute time point postdose in cohort 6)
- ± 1 hour on subsequent days in-house
- per the visit windows through end of study

8.2.1 General Assessments

8.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.1.2 Demographics

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

8.2.1.3 Medical History

A complete medical history will be obtained at screening by the investigator or designated site physician. Medical history will include information on the subject's current health, psychiatric, and surgical history. Relevant medical history findings will be recorded in the subject's source notes and on the appropriate pages of the CRF. Any unresolved medical history will be graded according to Clinical Adverse Event Severity Grading Scale and is described in Section 11.4.

8.2.1.4 Physical Examination

The investigator or designated site physician will perform a complete physical examination (excluding breast, genital, and rectal examination) at time points specified in the Schedule of Activities (**Section 1.3**). The neurological exam is included as part of the physical exam in cohorts 7 **to** 10 **and cohorts 12 to 13** (**Section 1.3**) and will include peripheral sensory and motor evaluation, and assessment of gait, pain, position, strength**,** and reflexes.

Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.1.5 Physical Measurements

Height in centimeters should be measured without shoes. Subjects should be in a clinic gown and without shoes each time body weight in kilograms is measured. Weight is measured twice, with accepted values within 0.1 kg. Body mass index should be calculated using the following formula:

body mass index (kg/m^2) = weight (kg)/[height (cm)/100]^2.

Waist circumference: Subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line, and also marked. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the same procedure throughout the study. The reading is taken to the nearest centimeter and entered in the source document.

8.2.1.6 Substance Abuse History

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

8.2.2 Safety Assessments

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

8.2.2.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

8.2.2.2 Suicidal Risk Monitoring

Baseline assessment of suicidal ideation and behavior, and treatment-emergent suicidal ideation and behavior will be monitored during the study using C-SSRS and Patient PHQ-9. The C-SSRS is a clinician rating of suicidal behavior and ideation. The

C-SSRS consists of a maximum of 20 items. Columbia Suicide Severity Rating Scale will be administered in study subjects at each study visit to assess possible suicidal ideation and behavior. Reports of suicidal ideation with intent to act (endorse item 4 or 5) and reports of actual, aborted, or interrupted suicide attempts or a behavior preparatory for making an attempt indicate subjects at high risk for suicide. If such reports are identified, the investigator is to appropriately manage the subject in accordance with standard of care. AMG 133 will be discontinued in subject who experience signs of suicidal ideation or behavior. Refer to Sections 11.8 through Section 11.10 for more information on mental health monitoring.

8.2.2.3 Electrocardiograms

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECGs should be performed in a standardized method, in triplicate, and run consecutively (all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third), before blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

As required per Section 1.3:

- Single ECG at Screening
- 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (all 3 ECGs should be completed within a total of 5 minutes from the start of the first to the completion of the third) (total 9 ECGs)
- Triplicate ECGs at time points after dosing

Baseline is defined as day 1 predose. The primary investigator or (eg, designated site physician) will review all ECGs. The ECGs will be transferred electronically to an ECG central vendor for storage and archiving per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen, or designee. Standard ECG machines should be used for all study-related ECG requirements. In certain circumstances Amgen may be able to provide a standard ECG machine if a site is unable to provide **one**.

[redacted]

8.2.2.5 Neurologic assessments

Neurological exams are incorporated as part of the safety assessments in the multiple dose phase (Part B **and Part C**) of the current study. The neurological exam will be conducted as part of the physical exam and will include peripheral sensory and motor evaluation, and assessment of gait, pain, position, strength, and reflexes.

8.2.3 Adverse Events and Serious Adverse Events

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

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

8.2.3.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Amgen Standard Grading Scale and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the 30 (+3) days of last dose of investigational product or end of study, whichever is later are reported using the Event CRF.

As an industry-wide standard practice, the study site staff (whether experienced it him/herself or experienced/reported by a study participant) is advised to communicate an adverse event and/or a product complaint associated * with the non-Amgen wearable device to the legal manufacturer of that device as soon as possible.

*Note: By association means that an adverse event demonstrates temporal and/or spatial associations with the non-Amgen wearable device. Please refrain from including further adjudication of such events in the communications to the device manufacturer and the expectedness of the event by investigators and by Amgen safety medical reviewers.

8.2.3.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 (+3) days of last dose of investigational product or end of study, whichever is later are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

8.2.3.1.3 Serious Adverse Events After the Protocol-required Reporting Period

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

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

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

8.2.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

8.2.3.3 Follow-up of Adverse Events and Serious Adverse Events

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

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

8.2.3.4 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 Amgen.

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

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

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

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

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

8.2.3.5 Safety Monitoring Plan

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

8.2.3.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until 5 months after receiving the last dose of investigational product.

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 Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

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

8.2.4 Clinical Laboratory Assessments

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

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Events CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Pregnancy Testing

Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject,

becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

A pregnancy test should be performed according to the Schedule of Activities (**Section 1.3**) including the end of study/safety follow-up visit after discontinuing protocol-required therapies.

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

8.2.5 Pharmacokinetic Assessments

All subjects randomized to AMG 133 will have pharmacokinetic samples assessed.

Whole blood samples of approximately 5 mL will be collected for measurement of plasma concentrations of AMG 133 as specified in the Schedule of Activities (**Section 1.3**). A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Whole blood samples [redacted] will be collected by venipuncture or cannulation at the times indicated in the Schedule of Activities (**Section 1.3**).

8.2.6 Pharmacodynamic Assessments

Venous blood samples of approximately 5 to 7.5 mL will be collected for measurement of AMG 133 treatment pharmacodynamic effects at each time point specified in the Schedule of Activities (**Section 1.3**). [redacted]

8.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on

inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of metabolic disorders, such as obesity, and/or to identify subjects who may have positive or negative response to AMG 133. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted from samples taken during the study.

The final disposition of samples will be described in Section 11.6.

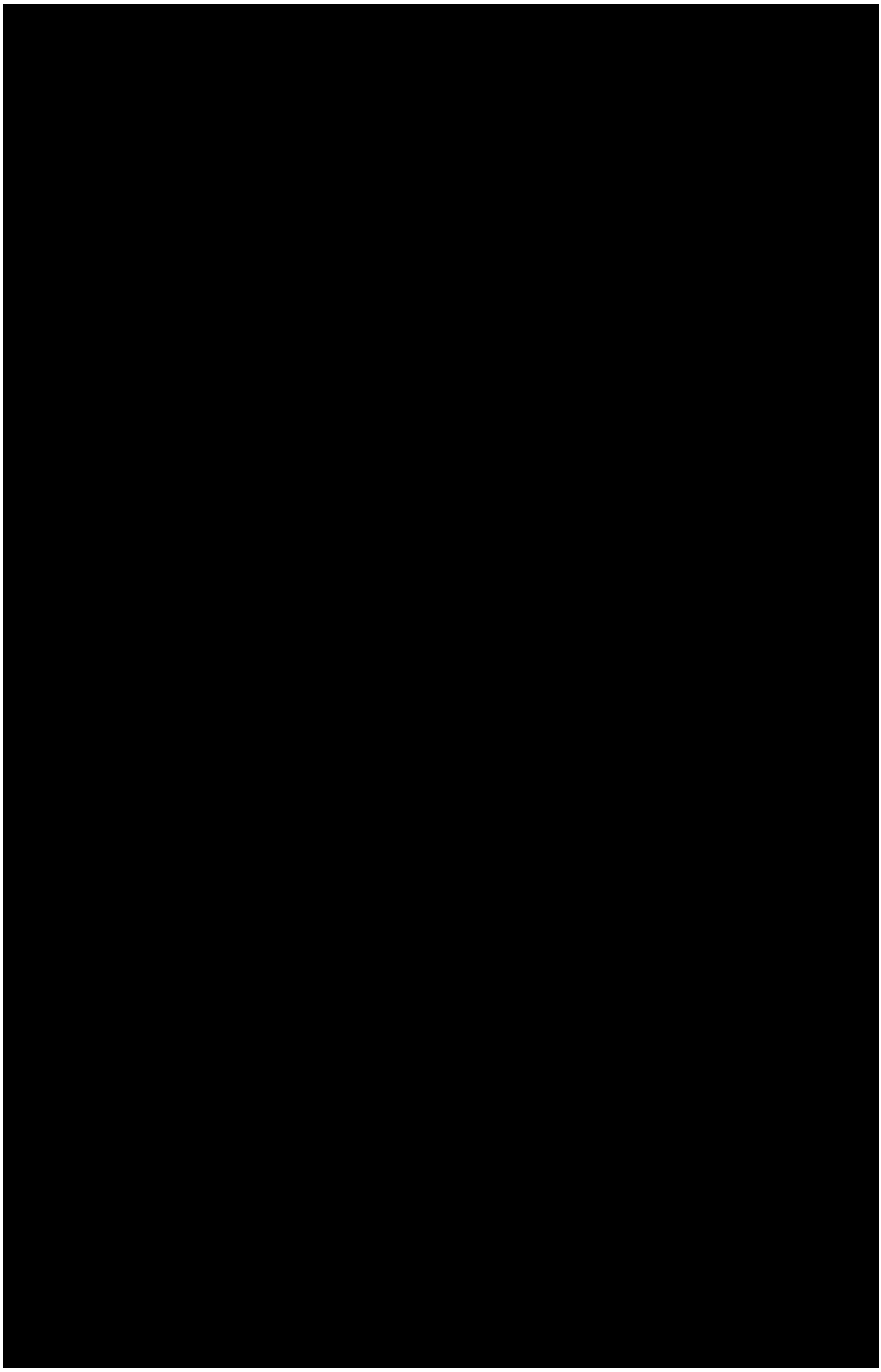
8.2.8 Antibody Testing Procedures

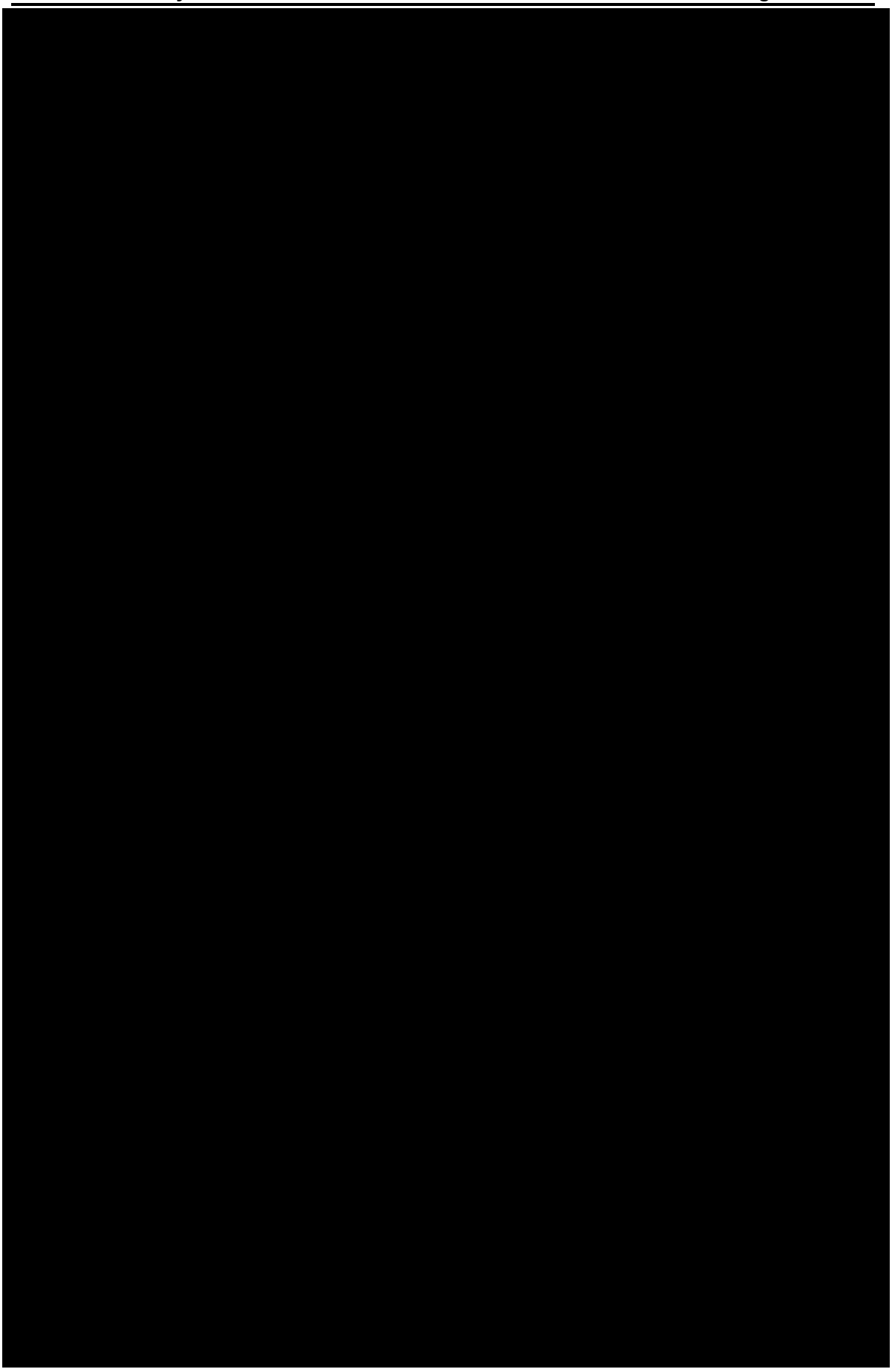
Blood samples for antibody testing are to be collected as outlined in the Schedule of Activities (**Section 1.3**). Bioanalytical testing for anti-AMG 133 antibodies will be conducted on these samples using a fully validated, electrochemiluminescence-based immunoassay. All samples that test positive for ADA will be tittered 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 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. 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.

8.2.9 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

[redacted]





9. Statistical Considerations

9.1 Statistical Hypotheses

No statistical hypotheses will be tested in this study.

9.2 Sample Size Determination

The sample size for the study is based on practical considerations. No statistical hypotheses will be tested. Approximately **112** subjects will be enrolled in the study, with 8 subjects per cohort (for cohort**s** 1 to 9 and cohort 11)**, up to** 20 subjects in cohort 10**, and up to 12 subjects from Part C with up to 6 subjects per cohort (for cohorts 12 to 13)**. Additional subjects may be enrolled if a DLRT recommendation is made to expand, repeat, or add cohorts to the study **or if replacement subjects are needed**.

For safety considerations, with up to **87** subjects (42 subjects from cohorts 1 to 6 and cohort 11 of Part A, 18 subjects from cohorts 7 to 9 of Part B, **up to** 15 subjects from cohort 10 of Part B**, and up to 12 subjects from cohorts 12 and 13 in Part C**) receiving AMG 133, there is at least **92.9**% chance of detecting an adverse event with a true incidence rate of 3% or greater and at least **98.8**% chance of detecting an adverse event with a true incidence rate of 5% or greater.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

9.3.1.1 Full analysis Set

The full analysis set will consist of all randomized subjects who receive at least 1 dose of AMG 133.

9.3.1.2 Safety Analysis Set

The safety analysis set is the same as the full analysis set.

9.3.1.3 Pharmacokinetic Analysis Set

The pharmacokinetics analysis set will consist of all subjects who received at least 1 dose of AMG 133 for whom at least 1 pharmacokinetics parameter or endpoint can be adequately estimated.

9.3.2 Covariates

Baseline values may be used as a covariate in analyses.

9.3.3 Subgroups

No subgroup analyses are planned.

9.3.4 Handling of Missing and Incomplete Data

The frequency of missing and incomplete data is expected to be low in this study and therefore, missing data will not be imputed. Methods for handling incomplete dates will be covered in the statistical analysis plan.

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported after the end of study, as defined in Section 4.4.1.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

The DLRM members will oversee progress of the study and make recommendations relating to early closure/extension or alteration of the study based on ongoing monitoring of the study data. Refer to Section 11.3 for further details.

The first administrative interim analysis will be conducted after the DLRM for cohort 9 with no preplanned adaptive decisions. This analysis will include data from cohorts 1 **to** 9. If cohorts 10 and 11 have undergone DLRM prior to the DLRM for cohort 9, data from these cohorts should be included in the analysis as well. For the **first** interim analysis, the data cutoff is 36 days after cohort 9 enrollment. At that time, the database will be cleaned, processed, and a snapshot for cohorts 1 **to** 9 will be taken and an “as is” snapshot for cohorts 10 and 11. The **first** interim analysis will assess the primary endpoints (subject incidence of treatment-emergent adverse events and changes in laboratory safety tests, vital signs, and 12-lead ECGs), secondary endpoints

(pharmacokinetic parameters and incidence of anti-AMG 133 antibody formation), and the following exploratory endpoints: [redacted] **The** study will be unblinded to sponsor staff conducting and reviewing the interim analysis and remain blinded to site personnel and site-facing staff of the sponsor.

The second interim analysis will occur after all subjects in cohorts 1 to 11 have completed the study. For the second interim analysis, the data cutoff is at EOS. At that time, the database will be cleaned, processed, and a snapshot for cohorts 1 to 11 will be taken. The second interim analysis will include all time points and all planned analysis similar to the final analysis with the exception that the data generated [redacted] will not be included in the second interim analysis but will be included in the final analysis instead. The study will be unblinded to sponsor staff conducting and reviewing the interim analysis and remain blinded to site personnel and site-facing staff of the sponsor.

9.4.1.2 Primary Analysis

The primary analysis will occur at the final analysis and not be a separate analysis.

9.4.1.3 Final Analysis

The final analysis will occur after all subjects in cohorts 1 **to** 1**3** have completed this study. Data will be locked prior to conducting the final analysis based on a clean snapshot of data from cohorts 1 **to** 1**3**.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, pharmacokinetic, and pharmacodynamic endpoints. Accumulating pharmacodynamic data might be reviewed throughout the study by treatment, periodically. Descriptive statistics on continuous measurements will include means, medians, 25th and 75th percentiles, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Pharmacokinetic, pharmacodynamic, and clinical laboratory data will be summarized by treatment group and at each time point when samples are collected. Graphical summaries of the data may also be presented.

Data for subjects receiving placebo will be combined across cohorts 1 to 5 and cohort 11 (SC) and cohort 6 (IV), except for adverse events where the combined SC cohorts will be summarized separately from the IV cohort within Part A.

Data for subjects receiving the placebo will be combined across cohorts 7 **to** 9 within Part B and data for subjects receiving placebo from cohort 10 will be summarized separately. **Part C is an open-label study, therefore, data for subjects from cohorts 12 to 13 will be summarized separately.**

Data for subjects receiving AMG 133 will be presented separately by cohort. When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used.

9.4.2.2 Efficacy Analyses

Efficacy will not be assessed in this study.

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	• Subject incidence of treatment-emergent adverse events including fatal adverse events, serious adverse events, and adverse events leading to withdrawal from investigational product or other protocol-required therapies. • Summary statistics of safety laboratory test results including summary statistics at each protocol scheduled visit by cohort/combined placebo cohort. • Summary statistics of vital signs including summary statistics at each protocol scheduled visit by cohort/combined placebo cohort. • Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

9.4.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by 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 treatment-emergent adverse events will also be provided. The number and percentage of subjects reporting adverse events will be evaluated for each dose cohort, across dose cohorts, and will also be tabulated by relationship to study drug. Adverse events resulting in treatment discontinuation will be identified.

9.4.2.3.3 Laboratory Test Results

Hematology, chemistry, and urinalysis data will be reviewed for each subject. Values outside the normal laboratory reference range will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided.

9.4.2.3.4 Vital Signs

Vital signs will be reviewed for each subject. Summaries of heart rate and blood pressure data over time and change from baseline will be provided.

9.4.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics at each protocol scheduled visit by cohort/combined placebo cohort.

9.4.2.3.6 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QT interval corrected for heart rate using Fridericia's formula will be categorized, and the number and percentage of subjects in each group will be summarized. Subjects' maximum postbaseline values will also be categorized, and the number and percentage of subjects in each group will be summarized. All on study ECG data will be listed and select parameters of interest will be plotted.

9.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 133 antibodies (binding and if positive, neutralizing **to native GLP1**, when available) at any time will be tabulated by treatment group.

9.4.2.3.8 Exposure to Investigational Product

The number of doses of investigational product and the proportion of subjects receiving each dose level will be summarized using descriptive statistics. Subject-level data may be provided instead of the summary if the subject incidence is low or single dose is given.

9.4.2.3.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each cohort/combined placebo cohort as coded by the World Health Organization Drug dictionary.

9.4.2.4 Other Analyses

9.4.2.4.1 Secondary Endpoint — Pharmacokinetics Analysis

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 cohort. Pharmacokinetic parameters that may include, but are not limited to AUC, C_{max}, and t_{max} will be estimated using either compartmental (eg, pharmacokinetic modeling) or noncompartmental methods. Actual dosing and sampling times will be used for calculation of pharmacokinetic parameters. Summary statistics will be generated for each pharmacokinetic parameter for each dose cohort.

A power model will be used to examine dose/concentration relationship over the SC cohorts. The dependent variable will be ln(AUC) or $\log_e(C_{max})$ and the independent variable will be $\log_e$(dose).

[redacted] test will be determined using a validated assay. Individual plasma concentration-time plots will be presented for each subject as well as mean concentration-time plot for each dose cohort. Pharmacokinetic parameters that may include, but not limited to AUC from 0 to 5 hours as well as C_{max} and t_{max}.

9.4.2.4.2 Exploratory Endpoints

The statistical analyses in this section are considered exploratory in nature and will be performed only when deemed appropriate.

10. References

Althage MC, Ford EL, Wang S, et al, Targeted ablation of glucose-dependent insulinotropic polypeptide-producing cells in transgenic mice reduces obesity and insulin resistance induced by a high fat diet. *J Biol Chem*. 2008;283:18365-18376.

AMG 133 Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

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.

Berndt SI, Gustafsson S, Magi R, et al, Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nat Genet*. 2013;45:501-512.

Dalle Grave R, Calugi S, Molinari E, et al, Weight loss expectations in obese patients and treatment attrition: an observational multicenter study. *Obes Res*. 2005;13:1961-1969.

Drucker, DJ. (2006). The biology of incretin hormones. *Cell Metab* 3, 153-165.

Hauner H, Glatting G, Kaminska D, Pfeiffer EF. Effects of gastric inhibitory polypeptide on glucose and lipid metabolism of isolated rat adipocytes. *Ann Nutr Metab*. 1988;32:282-288.

Heymsfield SB, Wadden TA. Mechanisms, pathophysiology and management of obesity. *N Engl J Med*. 2017;376:254-266.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. http://www.icmje.org/

International Council for Harmonisation. International Council for Harmonisation (ICH) Harmonised Tripartite Guideline: Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals S6 (R1), 2011.

Jensen MD, Ryan DH, Apovian CM, et al, 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(Suppl 2):S102–S138.

Khera R, Murad MH, Chandar AK, et al, Association of pharmacological treatments for obesity with weight loss and adverse events. *JAMA*. 2016;315:2424.

Killion EA, Wang J, Yie J, Shi SD, et al, Anti-obesity effects of GIPR antagonists alone and in combination with GLP-1R agonists in preclinical models. *Sci Transl Med.* 2018;10:472.

Knapper JM, Puddicombe SM, Morgan LM, Fletcher JM. Investigations into the actions of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1(7-36)amide on lipoprotein lipase activity in explants of rat adipose tissue. *J Nutr*. 1995;125:183-188.

Kolotkin RL, Meter K, Williams GR. Quality of life and obesity. *Obes Rev* 2001;2:219-229.

Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, et al, Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med.* 2013;369:145-154.

Look AHEAD Research Group. 8-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity (Silver Spring)*. 2014;22:5-13.

Miyawaki K, Yamada Y, Ban N, et al, Inhibition of gastric inhibitory polypeptide signaling prevents obesity. *Nat Med*. 2002;8:738-742.

Nasteska D, Harada N, Suzuki K, et al, Chronic reduction of GIP secretion alleviates obesity and insulin resistance under high-fat diet conditions. *Diabetes*. 2014;63:2332-2343.

Okada Y, Kubo M, Ohmiya H, et al, Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat Genet*. 2012;44:302-306.

Saxena R, Hivert MF, Langenberg C, et al, Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nat Genet*. 2010;42:142-148.

Speliotes EK, Willer CJ, Berndt SI, et al, Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42:937-948.

Terranova L, Busetto L, Vestri A, Zappa MA. Bariatric surgery: cost-effectiveness and budget impact. *Obes Surg*. 2012;22:646-653.

Turton MD, O'shea D, Gunn I, Beak SA, Edwards CM, Meeran K, CHO-K1i SJ, et al, A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature*. 1996;379:69.

United States Food and Drug Administration. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005.

Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 2011;378:815-825.

Wen W, Cho YS, Zheng W, et al, Meta-analysis identifies common variants associated with body mass index in east Asians *Nat Genet*. 2012;44:307-311.

World Health Organization. Obesity and overweight; 2018 [cited 2019 September 18]. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/.

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

11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADA	antidrug antibodies
AUC	area under the concentration-time curve
AUC_{inf}	area under the plasma concentration time curve from time zero to infinity
AUC_{tau}	area under the concentration-time curve during a dosing interval defined here from time after 3rd dose to day 57
BIL	bilirubin
BMC	body mineral content
cAMP	cyclic adenosine monophosphate
CFR	U.S. Code of Federal Regulations
CHO	Chinese hamster ovary
C_{max}	maximum observed drug concentration during a dosing interval
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CVD	cardiovascular disease
day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
DILI	drug-induced liver injury
DIO	diet-induced obese
DLRM	dose level review meeting
DLRT	dose level review team
[redacted]	
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
EDC	electronic data capture
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study (EOS)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early

Enrollment	defined as when the investigator decides that the subject has met all eligibility criteria and assigns a randomization number
[redacted]	
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	glucagon-like peptide 1 receptor
GSO	global safety officer
HbA1c	hemoglobin A1c
[redacted]	
HRT	hormone replacement therapy
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IRT	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
IV	intravenous
Kd	dissociation constant
[redacted]	
mAb	monoclonal antibody
MAD	multiple ascending dose
[redacted]	
MRSD	maximum recommended starting dose
NCT	National Clinical Trials
NOAEL	no observed adverse effect level
PHQ-9	Patient Health Questionnaire-9
PD	pharmacodynamics
PK	pharmacokinetics
QTc	corrected QT interval
QW	**every week**
Q4W	every 4 weeks

Randomization	defined as once a unique subject randomization number has been assigned through IRT at enrollment
[redacted]	
SAD	single ascending dose
SC	subcutaneous
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
TBL	total bilirubin
t_{max}	time of maximum observed concentration
ULN	upper limit of normal

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12 will be performed by the central laboratory and/or by the local laboratory.

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

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

Table 12. Analyte Listing

Local Laboratory: Chemistry	Local Laboratory:	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology[c]	Central Laboratory: Other Labs
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Adjusted calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Uric acid Total bilirubin Direct bilirubin ALP LDH AST (SGOT) ALT (SGPT) CRP **(cohort 10), or CRP-HS (cohorts 7 to 9 and 12 to 13)** Calcitonin (screening only) Amylase Lipase Creatine kinase Tryptase (in the event of a suspected anaphylactic reaction) TSH (screening only)	<u>Drug Screen</u> Benzodiazepines Barbiturates Opiates Tetrahydrocannabinol Cocaine Amphetamines Ethanol (may be performed by a breath test) Cotinine <u>Viral Panel</u> Hep B surface antigen Hep B Core Antibody Hep C antibody HCV RNA PCR (as necessary) HIV[a] <u>Reproductive</u> Serum or Urine Pregnancy FSH [redacted]	APTT PT/INR	Specific gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial cells Bacteria Casts Crystals	RBC Nucleated RBC Hemoglobin Hematocrit MCV MCH MCHC RDW Reticulocytes Platelets WBC total WBC Differential • Bands/stabs • Eosinophils • Basophils • Lymphocytes • Monocytes • Segmented neutrophils • Total neutrophil count	Antibodies <u>Plasma PK</u> • AMG 133 [redacted] Safety assessments [redacted]

[a] HIV assessment is recommended.

[redacted]

[c.] **Total neutrophils should be reported unless there are bands/stabs listed; then bands/stabs and segmented neutrophils should be reported.**

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; **CRP-HS = C-reactive protein-high sensitivity;** [redacted]; CK = creatine kinase**;** FSH = follicle stimulating hormone; [redacted] HCV = hepatitis C virus; [redacted]; Hep = hepatitis; HIV = human immunodeficiency virus; [redacted] INR = international normalized ratio; LDH = lactate dehydrogenase; [redacted]; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PD = pharmacodynamics; PK = pharmacokinetics; PT = prothrombin time; [redacted]; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cell count

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

11.3 Appendix 3. Study Governance Considerations

Dose Level Review Meetings (DLRM)

A DLRM is conducted to review and interpret safety data for the purposes of making recommendations about dose-level escalation (either to the next planned dose or to an intermediate dose), dose level de-escalation, cohort continuation, or cohort expansion; making recommendations about non-dose escalation cohorts (eg, expanded, highest dose and/or final cohort); and evaluating safety signals for purposes of applying Dose Cohort Stopping Rules. The required Dose Level Review Team (DLRT) members are the medical monitor, Global Safety Officer (GSO), and Site Investigators. The DLRT will include actively screening and enrolling Site Investigators. The medical monitor, GSO, and Site Investigators are the only voting DLRT members. The following nonvoting Amgen representatives may also be part of the DLRT: clinical study manager, biostatistician, or pharmacokinetics scientist.

The medical monitor must be in attendance and cannot be represented by a voting designee or delegate. Voting designees can be identified as appropriate by the GSO or site investigator(s). A site investigator may identify a delegate (eg, sub-investigator) who is listed in the Delegation of Authority. If a site investigator does this, the site investigator must provide written agreement with the designee or delegate's vote.

For a DLRM to occur, the medical monitor must attend, and the GSO or delegate must attend. In addition, a quorum of Site Investigators must be present. A quorum is defined as more than 50% of the participating investigators or their qualified designees. The DLRM will be rescheduled if these requirements are not met.

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, electrocardiogram (ECG), vital signs, and laboratory results will be reviewed. Data to be reviewed will be unqueried.

Data will be reviewed blinded (ie, treatment assignment will not be revealed) unless unblinding is deemed necessary for the review team to make dosing recommendations. If deemed necessary, unblinding will be performed to assist dose change recommendations, in accordance with Amgen standard procedures.

Dose Level Review Meeting voting will occur as follows: there will be a total of 3 votes, 1 for the medical monitor, 1 for the GSO or delegate, and 1 for all of the Site Investigators or delegates combined. Regardless of how many Site Investigators there

are, all of the Site Investigators combined will have a total of 1 vote decided by a majority of the investigators (defined as greater than or equal to 50%).

Dose Level Review Meeting recommendations to escalate to the next planned cohort, or to an intermediate cohort, must be by unanimous vote. If the voting members of the DLRT are not able to reach a unanimous recommendation on whether to escalate to the next planned cohort or to an intermediate cohort, then this should be reflected in the DLRM Memo. Other recommendations, such as expanding a cohort or lowering a dose will be made by a majority vote.

Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

Informed Consent Process

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

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

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

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

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

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally 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; refer to Section 7.

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

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the 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 informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 28 days from the previous informed consent form signature date.

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

signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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

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

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

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

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

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

Publication Policy

To coordinate dissemination of data from this study, the investigator will obtain input and assistance from Amgen staff as appropriate.

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to

collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

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

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

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

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

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

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

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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

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

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

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

Source Documents

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

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

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

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

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

Elements to include:

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

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

Study and Site Closure

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

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

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

Compensation

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

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

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device**,** or procedure. • Note: Treatment-emergent adverse events will be defined in the statistical analysis plan.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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.
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 case report form (CRF). • The investigator must assign the following adverse event attributes: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); o Dates of onset and resolution (if resolved); o Did the event start prior to first dose of investigational product, other protocol-required therapies; o Assessment of seriousness; o Severity (or toxicity defined below); o Assessment of relatedness to investigational product, study-mandated procedures, and protocol-provided therapies; and/or study-mandated activity and/or procedures; o Action taken; and o Outcome of event. • If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization in lieu of completion of the Event CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • 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 Standard Grading Scale as show below:**	
Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity

SEVERE[a]	Incapacitating with inability to work or do usual activity

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

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product, study-mandated procedure, and/or protocol-mandated therapies 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 Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see Figure 11-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form. • **Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Report Form to report the event.**

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form

A **Study # 20180048** **AMG 133**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

Amgen Safety's US: +888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of 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	**Is event serious?**	**If serious, 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? AMG 133 No✓ Yes✓	**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

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

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

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

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

IP/Amgen Device:		**Date of Initial Dose** Day Month Year	**Prior to, or at time of Event** **Date of Dose** Day Month Year	**Dose**	**Route**	**Frequency**	**Action Taken with Product** 01 Still being Administered 02 Permanently discontinued 03 Withheld	**Lot # and Serial #**
AMG 133	☐ blinded ☐ Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*

Page 1 of 3

A **Study # 20180048** **AMG 133**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

	Site Number	Subject ID Number	

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

A **Study # 20180048** **AMG 133**	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

	Site Number	Subject ID Number	

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

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

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

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 5.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 5 months after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

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

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 5 months after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal, intrauterine device, intrauterine hormonal-releasing system, female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, postovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

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 5 months after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety 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 regions local privacy laws).
- After obtaining the female subject's signed authorization 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 5 months after the last dose of investigational product. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

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

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 5 months after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) 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 regions local privacy laws).
- The investigator will attempt to obtain a signed authorization 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 authorization 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 5 months after the last dose of investigational product.

- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 226.
- With the female subjects signed authorization 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 5 months after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20180048

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20180048

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

11.6 Appendix 6. Sample Storage and Destruction

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

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the obesity and other metabolic conditions, the dose response and/or prediction of response to AMG 133, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

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

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

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

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

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

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

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

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

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

Table 13. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

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

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

Permanent withholding criteria are met when AST/ALT > 3x ULN in the presence of no important alternative causes for elevated AST/ALT and/or TBL values AND 1 of the following 2 are met: TBL > 2X ULN OR > 1.5x (for subjects not on anticoagulation therapy.

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

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

If signs or symptoms recur with rechallenge, then AMG 133 is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 13) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate case report form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

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

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 13 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

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

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

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

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

A more detailed history of:

- Prior and/or concurrent diseases or illness
- Exposure to environmental and/or industrial chemical agents
- Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
- Prior and/or concurrent use of alcohol, recreational drugs and special diets
- Concomitant use of medications (including 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 considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

11.8 Appendix 8. Mental Health Criteria Stopping Rules: Suggested Actions and Follow-up Assessments

Subjects with an increase in score on either the Patient Health Questionnaire 9 (PHQ-9) and/or C-SSRS assessments may meet the criteria for permanent discontinuation of Amgen investigational product or other protocol-required therapies.

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

The following stopping rules apply to subjects for whom an increase in their PHQ-9 and/or C-SSRS scores have been identified.

Table 14. Conditions for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Changes in Mental Health Scores

Mental Health Assessment	Permanent Discontinuation
PHQ-9	≥ 10
	OR
C-SSRS	Answers yes to any items #1-5

PHQ-9 = Patient Health Questionnaire 9 ; C-SSRS = Columbia Suicide Severity Rating Scale

Reporting

To facilitate appropriate monitoring for signals of mental health changes according to the criteria specified in the above, require the following:

The event is to be reported to Amgen 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 Case Report Form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld permanently due to potential mental health changes as specified in Table 14 are to undergo a period of “close observation” until the subject’s care can be transferred to an appropriate mental health professional.

11.9 Appendix 9. Columbia Suicide Severity Rating Scale (C-SSRS)

Baseline Form (example shown below) is to be administered at screening visit and Since Last Visit Form at all subsequent visits by trained staff.

Figure 11-3. Sample C-SSRS Form

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐

If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

C-SSRS—Baseline (Version 1/14/09)
Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

C-SSRS—Baseline (Version 1/14/09) Page 2 of 2

11.10 Appendix 10. Patient Health Questionnaire 9 (PHQ-9)

Figure 11-4. Sample PHQ-9 Form

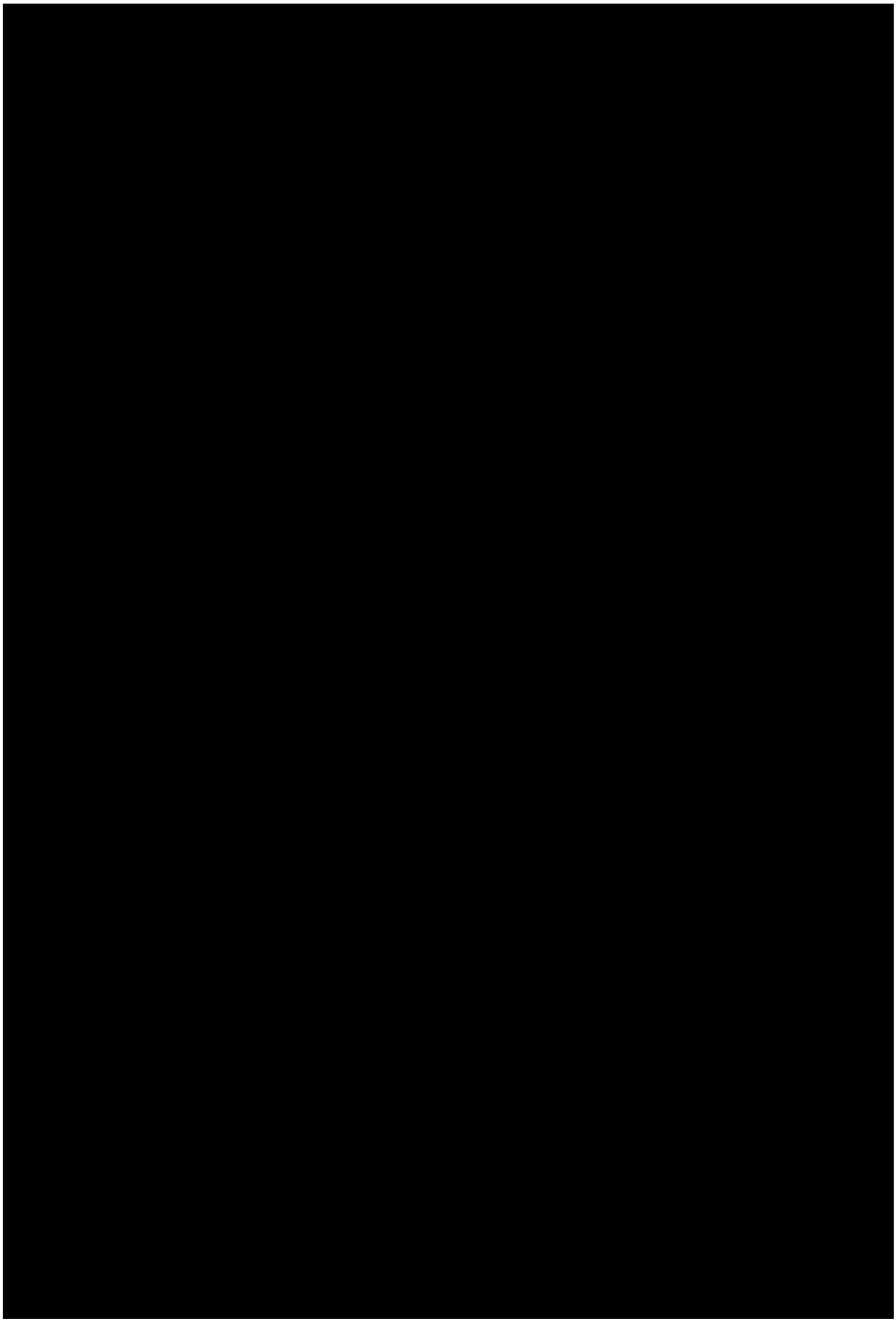
Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.



Amendment 4

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 133 in Subjects With Obesity

Amgen Protocol Number 20180048

Amendment Date: 03 February 2022

Rationale:

This protocol is being amended to:

- Update justification for investigational product dose, including estimated exposure.
- Add language to add flexibility to cohort 10 enrollment and change “20 subjects” to “up to 20 subjects.”
- Include [redacted] for cohort 10
- Add Part C (Cohorts 12 and 13) an open-label modified dose-escalation multiple ascending dose (MAD) cohorts in subjects with obesity.
- Update AMG 133 clinical experience.
- Add flexible language to allow for [redacted].
- Update inclusion and exclusion criteria to specify inclusion of cohorts 12 and 13, where applicable.
- Revise exclusion criterion #204 to include, “If ALT is $>$ 1.5 x the ULN at screening AND the AST, alkaline phosphatase, and total bilirubin levels are within normal limits, then subject may be eligible for enrollment after a discussion with the medical monitor.”
- Revise exclusion criterion #205 to include, “If a single value (PT, PTT, INR, or platelet count) is outside the normal reference range at screening and the subject

does not have evidence of any other bleeding or coagulation disorder, then the subject may be eligible for enrollment after a discussion with the medical monitor."

- Update investigational medical device language to allow use of an iPhone with cohorts 7 to 9.
- Update adverse event and serious adverse event reporting and product complaint language throughout protocol to align with current Amgen protocol template.
- Update language around interim analyses.
- Provide clarifying language surrounding laboratory tests in Table 12 Analyte Listing.
- Update "[redacted]."
- Provide clarifying language throughout for better site adherence and understanding.
- Make typographical, formatting, and editorial changes throughout the protocol.

Amendment 3

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 133 in Subjects With Obesity

Amgen Protocol Number (AMG 133) 20180048

Amendment Date: 14 May 2021

Rationale:

The following changes were made to the protocol, dated 14 May 2021 to add cohort 11 to further investigate the highest tolerable dose of AMG 133, to modify cohort 10 for added flexibility with dose selection, to add an interim analysis to assist with dose selection in phase 2 studies, and to clarify/correct other items in the protocol.

Cohort 11 changes include:

- Updated overall design (Section 1.1 and Section 4.1) and throughout the protocol to include cohort 11.
- Updated number of subjects (Section 4.2) to include cohort 11.
- Updated study Schema (Section 1.2) to include cohort 11.
- Updated justification for investigational product dose (Section 4.3) to include data currently available.
- Updated study treatments (Section 6.1.1), Table 8 to include cohort 11.
- Updated pharmacodynamic assessments (Section 8.2.6) to include cohort 11 and clarify parameters for the cohorts.

Cohort 10 changes include:

- Updated overall design (Section 1.1 and Section 4.1) to modify cohort 10 dose selection for flexibility.
- Updated justification for investigational product dose (Section 4.3) to include data currently available.

Interim analysis changes include:

- Updated Section 9.4.1.1 to include an interim analysis following the dose level review meeting for cohort 9.
- Updated Section 9.4.1.2 to indicate that the primary analysis will occur at the final analysis and not be a separate analysis.

Other changes include:

- Updated the clinical experience (Section 2.2.2.4) to include the data currently available.
- Modified inclusion criterion #103 to clarify ECG testing for cohorts prior to enrollment.
- Updated safety language with current template language.
- Administrative, typographical and formatting changes were made throughout the protocol.

Amendment 2

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 133 in Subjects With Obesity

Amgen Protocol Number 20180048

Amendment Date: 08 February 2021

Rationale:

This amendment is being made to add MAD study cohorts 7 to 10 to this ongoing study. This involves the following:

- Addition of cohorts 7-10
- The addition of the following [redacted] cohort 10 only
- Updated objectives and endpoints
- Administrative and editorial edits

Amendment 1

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 133 in Subjects With Obesity

Amgen Protocol Number 20180048

Amendment Date: 19 November 2020

Rationale:

This amendment is being made as a result of a response to the Food and Drug Administration (FDA) review of the investigational new drug application (IND) in addition to some omissions of lab collection that have been subsequently discovered and corrected. As such, the following changes have been made:

- Add creatine kinase as part of the serial clinical chemistry testing in screening and all other time points where clinical chemistry will be performed
- Extend end of study follow-up visits from 120 days to 150 days
- Update study duration
- Add that permanent withholding criteria are met when aspartate transaminase (AST)/alanine transaminase (ALT) > 3x upper limit of normal (ULN) in the presence of no important alternative causes for elevated AST/ALT and/or TBL values and 1 of the following 2 are met: Total bilirubin (TBL) > 2X ULN OR > 1.5x (for subjects not on anticoagulation therapy)
- Add amylase and lipase to day 15
- Add thyroid stimulating hormone (TSH) to screening