Title Page

Protocol Title:		A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 171 in Subjects With Obesity
Short Protocol Title:		Single and Multiple Ascending Dose Study of AMG 171 in Subjects With Obesity
Protocol Number:		20180224
Investigational Product:		AMG 171
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Protocol Version Date:		**Document Version** / **Date** Original / 14 October 2019 Protocol Amendment 1 / 07 February 2020 Protocol Amendment 2 / 28 October 2020 **Protocol Amendment 3 / 18 August 2021**
Data Elements Standards Version:		6.2

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 171 in Subjects With Obesity, dated **18 August 2021**, 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)

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 171 in Subjects With Obesity

Short Protocol Title: Single and Multiple Ascending Dose Study of AMG 171 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 significant side effects. AMG 171 is a long acting Fc fusion protein of Growth Differentiation Factor 15 (GDF15). In preclinical studies AMG 171 administration in obese cynomolgus monkeys resulted in an approximate 12% reduction in weight as compared to 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 and multiple ascending doses of AMG 171 as a potential therapy for the treatment of obesity.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of AMG 171 as single or 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 PK of AMG 171 as single or multiple doses in subjects with obesity	• AMG 171 PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (T_{max}), and area under the concentration time curve (AUC)
• To evaluate the immunogenicity of AMG 171	• Incidence of anti-AMG 171 antibody formation

Objectives	Endpoints
Exploratory	
• To characterize the PD effects of AMG 171 as single or multiple doses in subjects with obesity	• Changes in PD parameters:
○ To assess the effect of AMG 171 on fasting and post-prandial (Part A) metabolic parameters	○ Changes in the fasting and post-mixed meal challenge glucose, insulin, c-peptide, glucagon, and free fatty acid (FFA) concentrations
○ To assess the effect of AMG 171 on gastric emptying in the single ascending dose cohorts (Part A)	○ Gastric emptying as assessed by acetaminophen absorption kinetics (C_{max} and AUC)
○ To assess the effect of AMG 171 on fasting lipid levels	○ Changes in fasting lipid levels, including, but not limited to, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides
○ To assess the effect of AMG 171 on hemoglobin A1c (HbA1c) in the multiple dose cohorts (Part B)	○ Changes in HbA1c levels
○ To assess the effect of AMG 171 on potential biomarkers	○ Changes in potential biomarkers including, but not limited to, inflammatory and adipose tissue markers
○ To assess the effect of AMG 171 on endogenous GDF15 levels	○ Changes in endogenous GDF15 levels
○ To assess the effects of AMG 171 on body weight, waist circumference and body mass index (BMI)	○ Changes in body weight, waist circumference, and BMI
○ To assess the effect of AMG 171 on body composition in the multiple dose cohorts (Part B)	○ Changes in body composition as measured by whole body dual-energy x-ray absorptiometry (DXA)

Overall Design

This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple ascending dose study in adult subjects with obesity. The study will be conducted at approximately 3 - 4 sites in the United States. Additional sites may be added.
AMG 171 will be administered subcutaneously (SC). Part A is comprised of 2 single ascending dose (SAD) cohorts; Part B is a multiple dose cohort. Part C will be a titration phase with step dosing ranging from 2 to 3 ascending doses. **Part D will be a multiple ascending dose titration phase with step dosing ranging from 6 to 8 ascending doses.** The study consists of a total of **12** cohorts: 2 cohorts (Part A), 1 cohort (Part B), 3 cohorts (Part C)**, and 6 cohorts (Part D)**.

Potential subjects will be screened within 28 days before day 1 to assess their eligibility to enter the study. Subjects will be confined at the Clinical Research Unit (CRU) from Check-in (morning of **d**ay 1) through the morning of day 6 in Part A (SAD phase), from 1 day prior to each dose through the morning of day 6 for the first 2 doses in Part B, for each dose (2 to 3 doses) in Part C (titration phase)**, and for the first 3 days (2 nights) in Part D (multiple ascending dose titration phase)**.

Part A (SAD)

Seventeen subjects were enrolled into 2 cohorts (1 subject was replaced). No additional cohorts are planned for Part A. In each cohort, 8 subjects were randomized to receive AMG 171 or placebo SC (cohorts 1, 1b) in a 3:1 ratio as described in Table 1-1. For each cohort, the first 2 subjects (sentinel pair) were randomized such that 1 subject received AMG 171 and 1 subject received placebo. The sentinel pair was observed for at least 24 hours before the remaining subjects in the cohort were dosed after confirmation that there were no safety or tolerability concerns as assessed by the Principal Investigator. Enrollment into the SAD cohorts was sequential. Cohort 1b was dosed after the dose regimen in cohort 1 was deemed by the Dose Level Review Team (DLRT) to **have no safety signals observed** and **be** reasonably tolerated based on the safety and laboratory data through at least study day 15 for at least 7 out of 8 subjects dosed. The 2 SAD cohorts have completed dosing. Cohort 1 has reached study completion and cohort 1b has completed 3 months of follow-up. In Part A cohorts 1 and 1b tolerability was noted to worsen with the dose increase from [redacted] mg (cohort 1) to [redacted] mg (cohort 1b) with adverse events of nausea and vomiting (mild to moderate severity).

Part B (Multiple Ascending Dose [MAD])

Approximately 8 subjects will enroll into 1 cohort (cohort 2) where 8 subjects will be randomized to receive a total of 6 doses of [redacted] mg AMG 171 or placebo SC in a 3:1 ratio as described in Table 1-1. **No additional cohorts are planned for Part B.**

- Cohort 2: Study drug will be administered SC every 2 weeks (Q2W) for a total of six [redacted] mg doses.

Part C (Titration)

Approximately 24 subjects will enroll into 1 of 3 cohorts (cohorts 3 to 5). In each cohort, 8 subjects will be randomized to receive 2 to 3 consecutive doses of [redacted] mg AMG 171 or placebo SC in a 3:1 ratio as described in Table 1-1. Enrollment into cohort 3 will occur after DLRT recommendation based on safety and laboratory data through at least study day 22 of cohort 2 (Part B). Subsequently, cohorts 4 and 5 will be dosed in parallel after the dose regimen in cohort 3 has been recommended by the DLRT to **have no safety signals observed** and **be** reasonably tolerated based on safety and laboratory data through at least study day 22 for at least 6 out of 8 subjects dosed **and cumulative data of all prior cohorts**. Enrollment of dose cohorts is depicted in Figure 1-1**. No additional cohorts are planned for Part C**.

- Cohort 3: Two doses of study drug will be administered SC Q2W apart with the first dose of [redacted] mg and second dose of [redacted] mg.
- Cohort 4: Three doses of study drug will be administered SC Q2W apart with the first dose of [redacted] mg, second dose of [redacted] mg, and third dose of [redacted] mg.
- Cohort 5: Two doses of study drug will be administered SC Q1W apart with the first dose of [redacted] mg and second dose of [redacted] mg.

Part D (MAD Titration)

Approximately 48 subjects will enroll into 1 of 6 cohorts (cohorts 6a-c and 7a-c). In each cohort, 8 subjects will be randomized to receive 6 to 8 consecutive doses of AMG 171 or placebo SC in a 3:1 ratio as described in Section 1.3. The cohorts in group 6 will begin with [redacted] mg with dose escalation every 2 weeks while those in group 7 will begin with [redacted] mg with dose escalation weekly until the fourth dose ([redacted] mg) and then every other week thereafter. Enrollment into cohorts 6a and 7a will begin contemporaneously after a Dose Level Review Meeting (DLRM) of cohorts 4 and 5, which include review of cumulative data of all prior cohorts. Enrollment in cohorts 6b and 7b will occur after DLRT recommendation based on all safety and laboratory data through at least study day 43 of cohort 6a (Part D) and cumulative data of all prior cohorts. Subsequently, cohorts 6c and 7c will be dosed in parallel after the dose regimen in cohort 6b has been recommended by the DLRT to have no safety signals observed and be reasonably tolerated based on all safety and laboratory data through at least study day 57 for at least 6 out of 8 subjects dosed and cumulative data of all prior cohorts. Enrollment of dose cohorts is depicted in Figure 1-1.

- **Cohort 6a: Study drug will be administered SC Q2W for a total of 7 doses [redacted]**
- **Cohort 6b: Study drug will be administered SC Q2W for a total of 7 doses [redacted].**
- **Cohort 6c: Study drug will be administered SC Q2W for a total of 7 doses [redacted].**
- **Cohort 7a: Study drug will be administered SC Q1W for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].**
- **Cohort 7b: Study drug will be administered SC Q1W for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].**
- **Cohort 7c: Study drug will be administered SC Q1W for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].**

Dose Level Review Meetings (DLRM)

A DLRM will be held to review subject data and monitor safety before escalation to the next cohort. Escalation to a higher dose titration cohort will only proceed when the previous dose regimen and cumulative data from previous cohorts have been reviewed and found to **have no safety signals observed** and **be** reasonably tolerated based on available safety and laboratory data upon unanimous recommendation at the DLRM.

Safety and laboratory data will be reviewed **after** 7 of 8 subjects **have reached day 15 or 8 of 8 subjects have reached day 22 for each respective cohort** in Part A**,** B and C. **Safety and laboratory data will be reviewed through at least study day 43 of**

cohort 6a (Part D). Subsequently, cohorts 6c and 7c will be dosed in parallel after the dose regimen in cohort 6b has been recommended by the DLRT to have no safety signals observed and be reasonably tolerated based on all safety and laboratory data through at least study day 57 for at least 6 out of 8 subjects dosed and cumulative data of all prior cohorts.

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.

Number of Subjects

Approximately **96** subjects (8 subjects per cohort, cohorts 1, 1b, 2 to 5**, 6a-c, and 7a-c**) will be enrolled. Additional subjects may be enrolled if a DLRT recommendation is made to expand, repeat or add cohorts to the study.

Summary of Subject Eligibility Criteria

Subjects in the study will be males and females aged 18 to 65 years (inclusive) at the time of randomization with a BMI of ≥ 30.0 kg/m^2 and ≤ 40.0 kg/m^2. Females enrolled must be of non-reproductive potential.

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

Treatments

Cohorts 1-1b (Part A): After completion of all pre-dose procedures on the day of dosing, subjects in cohorts 1 and 1b received AMG 171 ([redacted]mg, respectively) or placebo SC on day 1. No additional cohorts are planned for Part A.

Cohort 2 (Part B): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 2 will receive AMG 171 [redacted]mg) or placebo SC Q2W x 6 on days 1, 15, 29, 43, 57, and 71.

Cohort 3 (Part C): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 3 will receive AMG 171 ([redacted]mg) or placebo SC on day 1, and AMG 171 [redacted]mg) or placebo SC on day 15.

Cohort 4 (Part C): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 4 will receive AMG 171 [redacted] mg) or placebo SC on day 1, and AMG 171 [redacted]mg) or placebo SC on day 15, and AMG 171 [redacted]mg) or placebo SC on day 29.

Cohort 5 (Part C): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 3 will receive AMG 171 [redacted] mg) or placebo SC on day 1, and AMG 171 [redacted]mg) or placebo SC on day 8.

The 2 cohorts in Part C (cohorts 4 and 5) will enroll in parallel.

Cohort 6a (Part D): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 6a will receive AMG 171 ([redacted]mg) or placebo SC on day 1; AMG 171 ([redacted]mg) or placebo SC on day 15; AMG 171 [redacted]mg) or placebo SC on day 29; and AMG 171 ([redacted]mg) or placebo SC on days 43, 57, 71, and 85.

Cohort 6b (Part D): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 6b will receive AMG 171 [redacted]mg) or placebo SC on day 1; AMG 171 ([redacted]mg) or placebo SC on day 15; AMG 171 [redacted]mg) or placebo SC on day 29; AMG 171 ([redacted]mg) or placebo SC on day 43; and AMG 171 [redacted]mg) or placebo on days 57, 71, and 85.

Cohort 6c (Part D): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 6c will receive AMG 171 [redacted]mg) or placebo SC on day 1; and AMG 171 [redacted]mg) or placebo SC on day 15; AMG 171 [redacted]mg) or placebo SC on day 29; AMG 171 [redacted]mg) or placebo SC on day 43; AMG 171

([redacted]mg) or placebo on day 57; and AMG 171 [redacted]mg) or placebo on days 71 and 85.

Cohort 7a (Part D): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 7a will receive AMG 171 [redacted]mg) or placebo SC on day 1; AMG 171 ([redacted]mg) or placebo SC on day 8; AMG 171 [redacted]mg) or placebo on day 15; AMG 171 ([redacted]mg) or placebo on day 22; AMG 171 [redacted]mg) or placebo on day 36; and AMG 171 ([redacted] mg) or placebo on days 50, 64, and 78.

Cohort 7b (Part D): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 7b will receive AMG 171 [redacted]mg) or placebo SC on day 1; AMG 171 [redacted]mg) or placebo SC on day 8; AMG 171 [redacted]mg) or placebo on day 15; AMG 171 [redacted]mg) or placebo on day 22; AMG 171 [redacted]mg) or placebo on day 36; AMG 171 [redacted]mg) or placebo on day 50; and AMG 171 [redacted]mg) or placebo on days 64 and 78.

Cohort 7c (Part D): After completion of all pre-dose procedures on the day of dosing, subjects in cohort 7c will receive AMG 171 [redacted]mg) or placebo SC on day 1; AMG 171 [redacted]mg) or placebo SC on day 8; AMG 171 [redacted]mg) or placebo on day 15; AMG 171 [redacted]g) or placebo on day 22; AMG 171 [redacted]mg) or placebo on day 36; AMG 171 [redacted]mg) or placebo on day 50; AMG 171 [redacted]mg) or placebo on day 64; and AMG 171 [redacted]mg) or placebo on day 78.

Table 1-1. Planned Dose Levels by Cohort in Parts A, B, and C

	Cohort	# Subjects	AMG 171/Placebo Dose/Frequency	Route	N (active: placebo)
PART A	1	8	[redacted] mg day 1 x 1	SC	6:2
	1b[a]	8	[redacted] mg day 1 x 1	SC	6:2
PART B (MAD)	2	8	[redacted] mg Q2W x 6	SC	6:2
PART C (titration)	3	8	[redacted] mg day 1 x 1 [redacted] mg day 15 x 1	SC	6:2
	4	8	[redacted] mg day 1 x 1 [redacted] mg day 15 x 1 [redacted] mg day 29 x 1	SC	6:2
	5	8	[redacted] mg day 1 x 1 [redacted] mg day 8 x 1	SC	6:2
PART D (MAD titration)	**6a**	**8**	**[redacted] mg day 1 x 1 [redacted] mg day 15 x 1 [redacted] mg day 29 x 1 [redacted] mg day 43 x 1 [redacted] mg day 57 x 1 [redacted] mg day 71 x 1 [redacted] mg day 85 x 1**	**SC**	**6:2**
	6b	**8**	**[redacted] mg day 1 x 1 [redacted] mg day 15 x 1 [redacted] mg day 29 x 1 [redacted] mg day 43 x 1**	**SC**	**6:2**

	Cohort	# Subjects	AMG 171/Placebo Dose/Frequency	Route	N (active: placebo)
			[redacted]mg day 57 x 1 mg day 71 x 1 mg day 85 x 1		
	6c	8	mg day 1 x 1 mg day 15 x 1 mg day 29 x 1 mg day 43 x 1 mg day 57 x 1 mg day 71 x 1 mg day 85 x 1	SC	6:2
	7a	8	mg day 1 x 1 mg day 8 x 1 mg day 15 x 1 mg day 22 x 1 mg day 36 x 1 mg day 50 x 1 mg day 64 x 1 mg day 78 x 1	SC	6:2
	7b	8	mg day 1 x 1 mg day 8 x 1 mg day 15 x 1 mg day 22 x 1 mg day 36 x 1 mg day 50 x 1 mg day 64 x 1 mg day 78 x 1	SC	6:2
	7c	8	mg day 1 x 1 mg day 8 x 1 mg day 15 x 1 mg day 22 x 1 mg day 36 x 1 mg day 50 x 1 mg day 64 x 1 mg day 78 x 1	SC	6:2

MAD = multiple ascending dose; Q2W = every 2 weeks; SC = subcutaneous.
[a] Cohort 1b added during protocol Amendment 1.

Procedures

Screening:

For all subjects, after informed consent is obtained, all screening procedures and tests establishing eligibility will be performed within 28 days before first dose of AMG 171 or placebo (day 1).

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

Serious Adverse Events (SAEs) will be collected from the time the Informed Consent Form (ICF) is signed.

In-House Residency

Subjects in Part A (cohorts 1 and 1b) were admitted after confirmed eligibility on day -2 for an 8-day (7-night) residency period.

Subjects in Part B (cohort 2) will be admitted after confirmed eligibility on day -1 for a 7-day (6-night) residency period and re-admitted on day 14 for a second 7-day (6-night) residency period.

Subjects in Part C (cohorts 3 to 5) will be admitted after confirmed eligibility on day -1.

Cohort 3 subjects will be admitted after confirmed eligibility on day -1 for a 7-day (6-night) residency period and re-admitted on day 14 for a second 7-day (6-night) residency period.

Cohort 4 subjects will be admitted after confirmed eligibility on day -1 for a 7-day (6-night) residency period, re-admitted on day 14 for a second 7-day (6-night) residency period, and re-admitted on day 28 for a third 7-day (6-night) residency period.

Cohort 5 subjects will be admitted after confirmed eligibility on day -1 for a 14-day (13-night) residency period.

Cohort 6 subjects will be admitted after confirmed eligibility on day -1 for a 2-day (1-night) residency period, re-admitted on days 14 and 28 for a 3-day (2-night) residency period, re-admitted on day 42 for a 7-day (6-night) residency period, and re-admitted on days 56, 70, and 84 for a 2-day (1-night) residency period.

Cohort 7 subjects will be admitted after confirmed eligibility on day -1 for a 3-day (2-night) residency period, and re-admitted on days 35, 49, 63, and 77 for a 3-day (2-night) residency period.

Day -2

Part A: Subjects who met all the screening inclusion criteria and none of the exclusion criteria were eligible to report to the research facility on day -2, at which time assessments were performed to confirm eligibility. Subjects that were deemed eligible after the completion of all day -2 assessments, were randomized to receive either AMG 171 or placebo on day 1.

Day -1

Part A: A Gastric Emptying test was performed on **d**ay -1 along with additional procedures as outlined in the Schedule of Activities in **Section 1.3**. As part of the Gastric Emptying test, subjects underwent an overnight fast of a minimum of 10 hours. Oral liquid acetaminophen 1000 mg (acetaminophen Extra Strength) was administered followed immediately by a standardized liquid meal (ie, 2 bottles or cans of Ensure Plus®). Timing of PK samples of acetaminophen after the standardized meal are summarized in the Schedule of Activities in **Section 1.3**.

Parts B**,** C**, and D**: 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 171 or placebo on day 1.

Day 1

After completion of all pre-dose procedures on the day of dosing (day 1), subjects will receive study drug (SC). Subjects will undergo vital signs and PK blood draws post-dose as outlined in the Schedule of Activities in **Section 1.3**.

Day 5

Part A: A Gastric Emptying test was repeated on day 5 along with additional procedures as outlined in the Schedule of Activities in **Section 1.3**.

Treatment and Follow-up

Subjects will return to the research facility as outlined in the Schedule of Activities and will undergo the following assessments at specified time points throughout the study: clinical laboratory evaluations, adverse event and serious adverse event collection, vital sign measurements, 12-lead ECGs, physical examinations, Gastric Emptying test (Part A only), Patient Health Questionnaire (PHQ-9), Columbia Suicide Severity Rating Scale (C-SSRS, Parts B**,** C**, and D**), DXA whole body composition assessments (Part B), PK, and other PD assessments. 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 EOS procedures on day 120 (Part A), day 207 (Part B), and a minimum of 70 days **or 60 days** after the last scheduled dose (Part**s** C **and D, respectively**).

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 Principal 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, PK and PD endpoints. Accumulating PD data might be reviewed throughout the trial 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, PD, 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 treatment.

The sample size for the study is based on practical considerations. No statistical hypothesis will be tested. For safety considerations, with up to **72** subjects (12 subjects from Part A, 6 subjects from Part B, 18 subjects from Part C**, and 36 subjects from Part D**) receiving AMG 171, the chance of detecting an adverse event with a true incidence rate of **2**% or greater is larger than **77**% and the chance of detecting an adverse event with a true incidence rate of **4**% or greater is larger than **95**%.

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

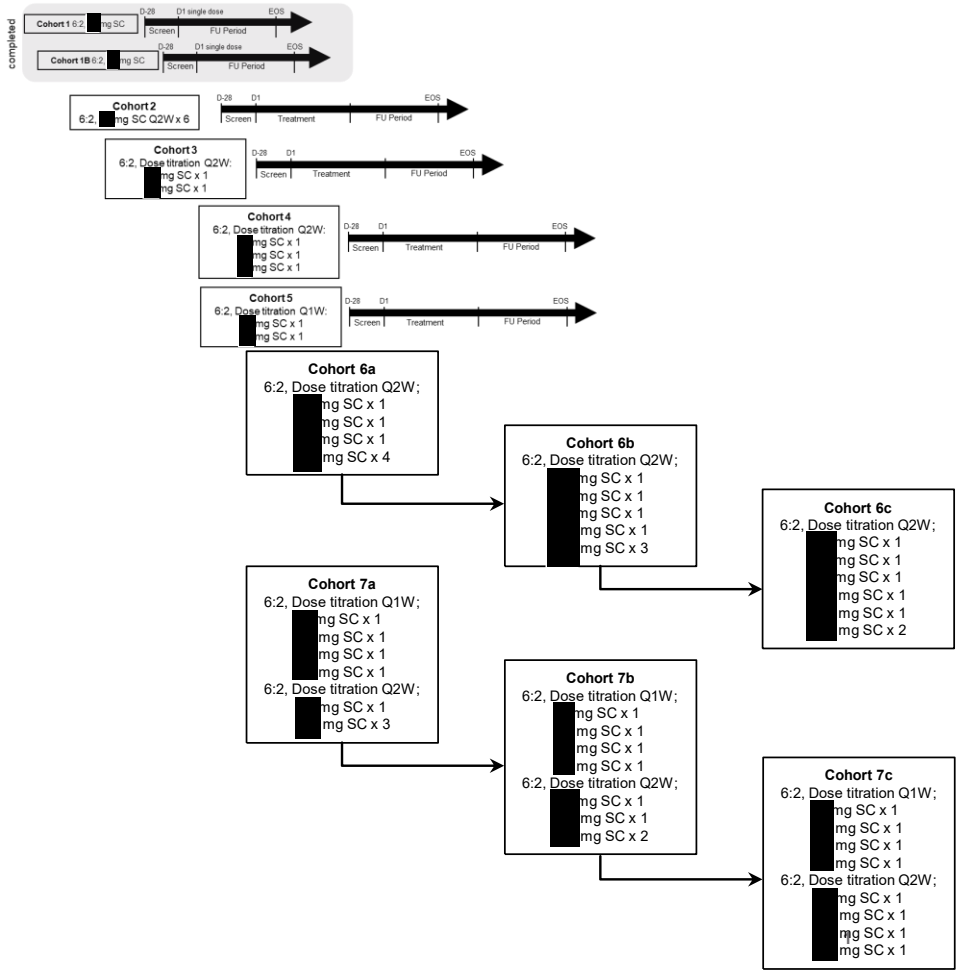
Statistical Hypotheses

No statistical hypotheses will be tested in this study.

Sponsor Name: Amgen, Inc.

1.2 Study Schema

Figure 1-1. Study Schema



EOS = end of study; FU = follow-up; Q1W = weekly; Q2W = every 2 weeks; SC = subcutaneous.

1.3 Schedule of Activities (SoA)

Table 1-2	Schedule of Activities Cohorts 1 and 1b (SAD)
Table 1-3	Schedule of Activities Cohort 2
Table 1-4	Schedule of Activities for Q2W Dose Titration – Cohort 3
Table 1-5	Schedule of Activities for Q2W Dose Titration – Cohort 4
Table 1-6	Schedule of Activities for Q1W Dose Titration – Cohort 5
Table 1-7	Schedule of Activities for Q2W Dose Titration – Cohort 6a
Table 1-8	Schedule of Activities for Q2W Dose Titration – Cohort 6b
Table 1-9	Schedule of Activities for Q2W Dose Titration – Cohort 6c
Table 1-10	Schedule of Activities for Q1W Dose Titration – Cohort 7a
Table 1-11	Schedule of Activities for Q1W Dose Titration – Cohort 7b
Table 1-12	Schedule of Activities for Q1W Dose Titration – Cohort 7c

Table 1-2. Schedule of Activities Cohorts 1 and 1b (SAD)

Period	Screening									Treatment																				EOS/ FU
Study Day	-28	-2	-1							1						2	3	4	5							6	15	22	29	43	57	71	92	120
Visit Windows																											± 1 day			± 3 day			± 7 days	
Time (in minutes)			0	30	60	90	120	180	300	0	10	60	120	240	480				0	30	60	90	120	180	300								
Time (in hours)[a]			0	0.5	1	1.5	2	2.5	5	0	0.16	1	2	4	8				0	0.5	1	1.5	2	2.5	5								
In-house residency[m]		←																								→							
Informed consent	X																																
Medical history	X																																
Demographics	X																																
Physical examination	X	X														X										X			X		X		X	X
C-SSRS + PHQ-9		X																	X														X
Body weight	X									X[b]									X							X	X	X	X	X	X	X	X	X
Height	X																																
Body Mass Index	X																																
Vital Signs (BP, HR, RR, TEMP)	X	X	X							X[b]				X	X	X	X	X	X						X	X	X	X	X	X	X	X	X	X
12-Lead ECG[c]	X	X								X[b, d]									X							X			X		X			X
Concomitant Medications	←																																→
Adverse Event Recording										→																							→
Serious Adverse Event Recording	←																																→
Clinical Chemistry[e,g]	X	X														X										X			X		X		X	X
Clinical Hematology[e]	X	X														X										X			X		X		X	X

Footnotes defined on last page of the table.

Table 1-2. Schedule of Activities Cohorts 1 and 1b (SAD)

Period	Screening									Treatment																						EOS/ FU
Study Day	-28	-2	-1							1						2	3	4	5							6	15	22	29	43	57	71	92	120
Visit Windows																											± 1 day			± 3 day			± 7 days	
Time (in minutes)			0	30	60	90	120	180	300	0	10	60	120	240	480				0	30	60	90	120	180	300								
Time (in hours)[a]			0	0.5	1	1.5	2	2.5	5	0	0.16	1	2	4	8				0	0.5	1	1.5	2	2.5	5								
Coagulation Tests[e]	X	X																														
eGFR[e]	X	X																														
Urinalysis[e]	X	X																	X									X				X
Alcohol, Cotinine and Drug Screen[e]	X	X																														
HIV, HBcAb, HBsAg, and HepCAb[e]	X																															
Pregnancy Test[e,h,j]	X	X[i]																														X
Serum FSH Test (Females Only)[e,k]	X																															
Gastric Emptying Test[o]			X[g]																X[g]													
DOSING																																
Study Drug Administration (SC)										X																						
BLOOD SAMPLES (± WINDOW)																																
Serum PK[f]										X[b]	X[n]	X	X	X	X	X	X	X	X							X	X	X	X	X	X	X	X
Plasma Acetaminophen PK[f,g]			X	X	X	X	X	X	X										X	X	X	X	X	X	X								
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X	X	X		X		X	X[b]									X	X	X		X		X				X				X
Serum PD (FFA)[f,g]			X	X	X		X		X	X[b]									X	X	X		X		X				X				X
Serum endogenous GDF15[f,g]										X[b]									X										X				X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides)[g,l]	X									X[b]									X										X				X

Footnotes defined on last page of the table.

Table 1-2. Schedule of Activities Cohorts 1 and 1b (SAD)

Period	Screening									Treatment																					EOS/ FU
Study Day	-28	-2	-1							1						2	3	4	5							6	15	22	29	43	57	71	92	120
Visit Windows																											± 1 day			± 3 day			± 7 days	
Time (in minutes)			0	30	60	90	120	180	300	0	10	60	120	240	480				0	30	60	90	120	180	300								
Time (in hours)[a]			0	0.5	1	1.5	2	2.5	5	0	0.16	1	2	4	8				0	0.5	1	1.5	2	2.5	5								
HbA1c[e]	X																																
Pharmacogenetic			X																														
Biomarker Development[g]			X																X									X					X
Anti-AMG 171 antibody										X[b]																	X		X					X

EOS = end of study; HIV = human immunodeficiency virus.
[a] Time in minutes/hours relative to the start time of standardized meal during Gastric Emptying test and start of each investigational product dose administration during Treatment and Follow-up periods
[b] Predose assessments
[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)
[d] 3 sets of triplicate ECGs at baseline (day 1 pre-dose)
[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons, as defined by the principal investigator
[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons, as defined by the principal investigator
[g] 10-hour fasting is required at all timepoints with the exception of timepoints following the standardized meal as part of the gastric emptying study
[h] Serum pregnancy test at screening and EOS (females only)
[i] Urine pregnancy test (females only)
[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] Serum FSH Test (female only) for postmenopausal status confirmation
[l] Local laboratory at screening, then central laboratory at other timepoints
[m] In-house residency day -2 to 6

Table 1-3. Schedule of Activities Cohort 2

Period	Screening		Treatment															Follow-up			EOS/FU
Study Day	**-28**	**-1**	**1**	**5**	**8**	**14**	**15**	**19**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**74**	**78**	**85**	**127**	**169**	**207**
Visit Windows																			± 1 day	± 3 days		
In-house residency[a]		X	X	X		X	X	X														
Informed consent	X																					
Medical history	X																					
Demographics	X																					
Physical examination	X	X								X[b]		X[b]		X[b]		X[b]			X	X		X
C-SSRS + PHQ-9	X	X								X[b]						X[b]			X	X		X
Body weight	X		X[b]	X	X		X[b]	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X	X	X	X	X
Height	X																					
Body Mass Index	X																					
Waist Circumference			X[b]							X[b]		X[b]		X[b]		X[b]			X			X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X	X	X	X[b]	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X	X	X	X	X
12-Lead ECG[c]	X	X	X[b,d]		X		X[b]			X[b]		X[b]		X[b]		X[b]			X			X
Concomitant Medications	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Adverse Event Recording			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious Adverse Event Recording	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Clinical Chemistry[e,g]	X	X	X[b]	X			X[b]			X[b]		X[b]		X[b]		X[b]			X	X	X	X
Clinical Hematology[e]	X	X	X[b]	X			X[b]			X[b]		X[b]		X[b]		X[b]			X	X	X	X
Coagulation Tests[e]	X																					
eGFR[e]	X	X																				
Urinalysis[e]	X																					
Alcohol, Cotinine and Drug Screen[e]	X																					
HIV, HBcAb, HBsAg, and HepCAb[e]	X																					
Pregnancy Test[h,j]	X	X[i]																				X
Serum FSH Test (Females Only)[k]	X																					
DOSING																						
Study Drug Administration (SC)			X				X			X		X		X		X						

Footnotes defined on next page of the table

Table 1-3. Schedule of Activities Cohort 2

Period	Screening		Treatment																Follow-up			EOS/FU
Study Day	-28	-1	1	5	8	14	15	19	22	29	36	43	50	57	64	71	74	78	85	127	169	207
Visit Windows																			± 1 day	± 3 days		
BLOOD SAMPLES (± WINDOW)																						
Serum PK[g]			X[b]	X	X	X	X[b]	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, and Glucagon)[f,g]			X[b]	X						X[b]				X[b]					X			X
Serum PD (FFA)[f,g]			X[b]	X						X[b]				X[b]					X			X
Serum endogenous GDF15[f,g]			X[b]	X						X[b]				X[b]					X			X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]							X[b]				X[b]					X			X
HbA1c[l]	X																		X			X
Pharmacogenetic			X[b]																			
Biomarker Development[g]			X[b]	X												X[b]			X			X
Anti-AMG 171 antibody[m]			X[b]				X			X[b]				X[b]					X			X
IMAGING																						
Whole body composition DXA Scan[n]		X																	X		X	

ECG = electrocardiogram; HIV = human immunodeficiency virus; DXA = Dual-Energy X-ray absorptiometry

[a] In-house residency day -1 to 6, and day 14 to day 20

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 pre-dose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by the principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by the principal investigator

[g] 10-hour fasting is required at all timepoints

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH Test (female only) for postmenopausal status confirmation

[l] Local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

[n] DXA scan may be performed within 3 days prior to day 1 and within ±3 days of day 85 and 169 visits

Table 1-4. Schedule of Activities for Q2W Dose Titration – Cohort 3

	Screening	Treatment																	Follow-up			EOS
Study Day	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**24**	**29**	**43**	**57**	**71**	**85**
Visit Windows									**± 1 day**								**± 1 day**		**± 1 day**	**± 3 days**		
In house residency[a]		X	X	X	X	X	X	X		X	X	X	X	X	X	X						
Informed consent	X																					
Medical history	X																					
Demographics	X																					
Physical examination	X	X	X[b]				X				X[b]				X			X	X			X
C-SSRS + PHQ-9	X	X																X				X
Body weight	X		X[b]		X			X	X		X[b]		X			X		X	X	X	X	X
Height	X																					
Body Mass Index	X																					
Waist Circumference			X[b]								X[b]							X	X			X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X		X		X	X	X	X[b]	X		X		X		X	X			X
12-Lead ECG[c]	X	X	X[b,d]					X			X[b]			X				X				X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]				X				X[b]				X			X		X		X
Clinical Hematology[e]	X	X	X[b]				X				X[b]				X			X		X		X
Coagulation Tests[e]	X																					
eGFR[e]	X	X																				
Urinalysis[e]	X																					
Alcohol, Cotinine and Drug Screen[e]	X																					
HIV, HBcAb, HBsAg, and HepCAb[e]	X																					
Pregnancy Test[h,j]	X	X[i]																				X
Serum FSH Test (Females Only)[k]	X																					
DOSING																						
Study Drug Administration (SC)			X								X											

Footnotes defined on next page of the table

Table 1-4. Schedule of Activities for Q2W Dose Titration – Cohort 3

	Screening	Treatment																	Follow Up			EOS
Study Day	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**24**	**29**	**43**	**57**	**71**	**85**
Visit Windows									**± 1 day**								**± 1 day**		**± 1 day**	**± 3 days**		
BLOOD SAMPLES (± WINDOW)																						
Serum PK[f]			X[b]	X	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]								X[b]							X				X
Serum PD (FFA)[f,g]			X[b]								X[b]							X				X
Serum endogenous GDF15[f,g]			X[b]								X[b]							X				X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]															X				X
HbA1c[l]	X																	X				X
Pharmacogenetic			X[b]																			
Biomarker Development[g]			X[b]								X[b]							X				X
Anti-AMG 171 antibody[m]			X[b]								X[b]							X		X		X

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ECG = electrocardiogram; HIV = human immunodeficiency virus**; Q2W = every 2 weeks**

[a] In-house residency day -1 to 6, and day 14 to day 20

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 predose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by the principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by the principal investigator

[g] 10-hour fasting is required at all timepoints

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH Test (female only) for postmenopausal status confirmation

[l] local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

Table 1-5. Schedule of Activities for Q2W Dose Titration – Cohort 4

	Screening	Treatment																							Follow up			EOS
Study Day	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**24**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**37**	**43**	**57**	**85**	**113**
Visit Windows									**± 1 day**								**± 1 day**								**± 1 day**	**± 3 days**			**± 5 days**
In house residency[a]		X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X					
Informed consent	X																												
Medical history	X																												
Demographics	X																												
Physical examination	X	X	X[b]				X				X[b]				X				X[b]				X			X			X
C-SSRS + PHQ-9	X	X																					X			X		X	X
Body weight	X		X[b]		X			X	X		X[b]		X			X	X		X[b]	X			X	X	X	X	X	X	X
Height	X																												
Body Mass Index	X																												
Waist Circumference			X[b]								X[b]								X[b]							X	X		X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X		X		X	X	X	X[b]	X		X		X	X		X[b]	X		X		X		X			X
12-Lead ECG[c]	X	X	X[b,d]			X		X		X	X[b]						X		X[b]							X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]				X				X[b]				X				X[b]				X			X			X
Clinical Hematology[e]	X	X	X[b]				X				X[b]				X				X[b]				X			X			X
Coagulation Tests[e]	X																												
eGFR[e]	X	X																											
Urinalysis[e]	X																												
Alcohol, Cotinine and Drug Screen[e]	X																												
HIV, HBcAb, HBsAg, and HepCAb[e]	X																												
Pregnancy Test[h,j]	X	X[i]																											X
Serum FSH Test (Females Only)[k]	X																												
DOSING																													
Study Drug Administration (SC)			X								X								X										

Footnotes defined on next page of the table

Table 1-5. Schedule of Activities for Q2W Dose Titration – Cohort 4

	Screening	Treatment																								Follow Up			EOS
Study Day	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**24**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**37**	**43**	**57**	**85**	**113**
Visit Windows									**± 1 day**								**± 1 day**								**± 1 day**	**± 3 days**			**± 5 days**
BLOOD SAMPLES (± WINDOW)																													
Serum PK[f]			X[b]	X	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]								X[b]								X[b]							X			
Serum PD (FFA)[f,g]			X[b]								X[b]								X[b]							X			
Serum endogenous GDF15[f,g]			X[b]								X[b]								X[b]							X			X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]								X[b]								X[b]							X			X
HbA1c[l]	X																									X		X	X
Pharmacogenetic			X[b]																										
Biomarker Development[g]			X[b]								X[b]								X[b]							X		X	
Anti-AMG 171 antibody[m]			X[b]								X[b]								X[b]							X		X	X

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ECG = electrocardiogram; HIV = human immunodeficiency virus**; Q2W = every 2 weeks**

[a] Optional in-house residency day -1 to 6, day 14 to day 20, and day 28 to day 34

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 pre-dose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by the principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by the principal investigator

[g] 10-hour fasting is required at all timepoints

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH test (female only) for postmenopausal status confirmation

[l] Local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

Table 1-6. Schedule of Activities for Q1W Dose Titration – Cohort 5

	Screening	Treatment																	Follow up			EOS
Study Day	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**17**	**22**	**29**	**43**	**57**	**71**	**85**
Visit Windows																	**± 1 day**		**± 3 days**			
In house residency[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Informed consent	X																					
Medical history	X																					
Demographics	X																					
Physical examination	X	X	X[b]				X			X[b]				X				X		X		X
C-SSRS + PHQ-9	X	X																X				X
Body weight	X		X[b]				X			X[b]				X				X		X		X
Height	X																					
Body Mass Index	X																					
Waist Circumference			X[b]							X[b]								X		X		X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X		X	X	X		X[b]	X		X	X	X			X		X		X
12-Lead ECG[c]	X	X	X[b,d]				X			X[b]				X				X				X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]				X			X[b]								X		X		X
Clinical Hematology[e]	X	X	X[b]				X			X[b]								X		X		X
Coagulation Tests[e]	X																					
eGFR[e]	X	X																				
Urinalysis[e]	X																					
Alcohol, Cotinine and Drug Screen[e]	X																					
HIV, HBcAb, HBsAg, and HepCAb[e]	X																					
Pregnancy Test[h,j]	X	X[i]																				
Serum FSH Test (Females Only)[k]	X																					
DOSING																						
Study Drug Administration (SC)			X							X												

Footnotes defined on next page of the table

Table 1-6. Schedule of Activities for Q1W Dose Titration – Cohort 5

	Screening	Treatment																Follow up			EOS
Study Day	**-28**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**17**	**22**	**29**	**43**	**57**	**71**	**85**
Visit Windows																	**± 1 day**		**± 3 days**			
BLOOD SAMPLES (± WINDOW)																						
Serum PK[f]			X[b]	X	X	X	X	X	X	X[b]	X	X	X	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]							X[b]								X		X		X
Serum PD (FFA)[f,g]			X[b]							X[b]								X		X		X
Serum endogenous GDF15[f,g]			X[b]							X[b]								X		X		X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]							X[b]								X		X		X
HbA1c[l]	X																	X		X		X
Pharmacogenetic			X[b]																			
Biomarker Development[g]			X[b]							X[b]								X		X		X
Anti-AMG 171 antibody[m]			X[b]							X[b]								X		X		X

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ECG = electrocardiogram; HIV = human immunodeficiency virus
[a] In house residency day -1 to day 14
[b] Predose assessments
[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)
[d] 3 sets of triplicate ECGs at baseline (day 1 predose)
[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by principal investigator
[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by principal investigator
[g] 10-hour fasting is required at all timepoints.
[h] Serum pregnancy test at screening and EOS (females only)
[i] Urine pregnancy test (females only)
[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] Serum FSH Test (female only) for postmenopausal status confirmation
[l] Local laboratory at screening, then central laboratory at other timepoints
[m] All ADA samples will be taken prior to dosing on days of dose administration

Table 1-7. Schedule of Activities for Q2W Dose Titration – Cohort 6a

	Screening	Treatment																								Follow-up			EOS
Study Day	-28	-1	1	2	4	12	13	15	17	19	22	29	33	43	45	47	49	52	57	71	85	86	88	90	93	99	113	127	141	155
Visit Windows											± 1 day																± 3 days			
In house residency[a]		X	X	X																										
Informed consent	X																													
Medical history	X																													
Demographics	X																													
Physical examination	X	X	X[b]			X		X[b]				X		X					X	X	X						X			X
C-SSRS + PHQ-9	X	X										X															X			X
Body weight	X		X[b]			X		X[b]				X		X					X	X	X						X			X
Height	X																													
Body Mass Index	X																													
Waist Circumference			X[b]					X[b]				X		X					X	X	X						X			X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X	X	X	X	X[b]				X		X					X	X	X						X			X
12-Lead ECG[c]	X	X	X[b,d]			X		X[b]				X		X					X	X	X									X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]			X		X[b]				X		X					X	X	X						X			X
Clinical Hematology[e]	X	X	X[b]			X		X[b]				X		X					X	X	X						X			X
Coagulation Tests[e]	X																													
eGFR[e]	X	X																												

Footnotes defined on next page of the table

Table 1-7. Schedule of Activities for Q2W Dose Titration – Cohort 6a

	Screening	Treatment																								Follow-up			EOS
Study Day	-28	-1	1	2	4	12	13	15	17	19	22	29	33	43	45	47	49	52	57	71	85	86	88	90	93	99	113	127	141	155
Visit Windows											± 1 day																± 3 days			
Urinalysis[e]	X																													
Alcohol, Cotinine, and Drug Screen[e]	X																													
HIV, HBcAb, HBsAg, and HepCAb[e]	X																													
Pregnancy Test[h,j]	X	X[i]																												
Serum FSH Test (Females Only)[k]	X																													
DOSING																														
Study Drug Administration (SC)			X					X				X		X					X	X	X									
BLOOD SAMPLES (± WINDOW)																														
Serum PK[f]			X[b]		X			X[b]		X		X[b]	X	X[b]	X	X	X	X	X[b]	X[b]	X[b]	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]					X[b]				X							X		X						X			X
Serum PD (FFA)[f,g]			X[b]					X[b]				X							X		X						X			X
Serum endogenous GDF15[f,g]			X[b]					X[b]				X							X		X						X			X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]					X[b]				X							X		X						X			X
HbA1c[l]	X											X							X		X						X			X
Pharmacogenetic			X[b]																											
Biomarker Development[g]			X[b]					X[b]			X																X			X
Anti-AMG 171 antibody[m]			X[b]					X[b]				X[b]															X			X

ADA = anti-drug antibody; BP = blood pressure; CSSR-S = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = epidermal growth factor receptor; EOS = end of study; FFA = free fatty acid; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1C; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HDL-C = high-density lipoprotein cholesterol; HepCAb = hepatitis C antibody; HIV = human immunodeficiency virus; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic(s); PHQ-9 = 9 question Patient Health Questionnaire; PK = pharmacokinetic(s); Q2W = every 2 weeks; SC = subcutaneous; TEMP = temperature.

[a] In house residency day -1 to day 2

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 predose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by principal investigator

[g] 10-hour fasting is required at all timepoints.

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH Test (female only) for postmenopausal status confirmation

[l] Local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

Table 1-8. Schedule of Activities for Q2W Dose Titration – Cohort 6b

	Screening	Treatment																									Follow-up			EOS
Study Day	-28	-1	1	2	4	12	13	15	17	19	22	29	33	43	47	57	59	61	63	66	71	85	86	88	90	93	99	113	127	142	155
Visit Windows											± 1 day																	± 3 days			
In house residency[a]		X	X	X																											
Informed consent	X																														
Medical history	X																														
Demographics	X																														
Physical examination	X	X	X[b]			X		X[b]				X		X		X					X	X						X			X
C-SSRS + PHQ-9	X	X										X																X			X
Body weight	X		X[b]			X		X[b]				X		X		X					X	X						X			X
Height	X																														
Body Mass Index	X																														
Waist Circumference			X[b]					X[b]				X		X		X					X	X						X			X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X	X	X	X	X[b]				X		X		X					X	X						X			X
12-Lead ECG[c]	X	X	X[b,d]			X		X[b]				X		X		X					X	X									X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]			X		X[b]				X		X		X					X	X						X			X
Clinical Hematology[e]	X	X	X[b]			X		X[b]				X		X		X					X	X						X			X
Coagulation Tests[e]	X																														

Footnotes defined on next page of the table

Table 1-8. Schedule of Activities for Q2W Dose Titration – Cohort 6b

	Screening	Treatment																										Follow-up			EOS
Study Day	-28	-1	1	2	4	12	13	15	17	19	22	29	33	43	47	57	59	61	63	66	71	85	86	88	90	93	99	113	127	142	155
Visit Windows											± 1 day																	± 3 days			
eGFR[e]	X	X																													
Urinalysis[e]	X																														
Alcohol, Cotinine, and Drug Screen[e]	X																														
HIV, HBcAb, HBsAg, and HepCAb[e]	X																														
Pregnancy Test[h,j]	X	X[i]																													
Serum FSH Test (Females Only)[k]	X																														
DOSING																															
Study Drug Administration (SC)			X					X				X		X		X					X	X									
BLOOD SAMPLES (± WINDOW)																															
Serum PK[f]			X[b]		X			X[b]		X		X[b]	X	X[b]	X	X[b]	X	X	X	X	X[b]	X[b]	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]					X[b]				X				X						X						X			X
Serum PD (FFA)[f,g]			X[b]					X[b]				X				X						X						X			X
Serum endogenous GDF15[f,g]			X[b]					X[b]				X				X						X						X			X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]					X[b]				X				X						X						X			X
HbA1c[l]	X											X				X						X						X			X
Pharmacogenetic			X[b]																												
Biomarker Development[g]			X[b]					X[b]			X																	X			X
Anti-AMG 171 antibody[m]			X[b]					X[b]				X[b]																X			X

ADA = anti-drug antibody; BP = blood pressure; CSSR-S = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = epidermal growth factor receptor; EOS = end of study; FFA = free fatty acid; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1C; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HDL-C = high-density lipoprotein cholesterol; HepCAb = hepatitis C antibody; HIV = human immunodeficiency virus; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic(s); PHQ-9 = 9 question Patient Health Questionnaire; PK = pharmacokinetic(s); Q2W = every 2 weeks; SC = subcutaneous; TEMP = temperature.

[a] In house residency day -1 to day 2

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 predose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by principal investigator

[g] 10-hour fasting is required at all timepoints.

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH Test (female only) for postmenopausal status confirmation

[l] Local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

Table 1-9. Schedule of Activities for Q2W Dose Titration – Cohort 6c

	Screening	Treatment																										Follow-up			EOS
Study Day	-28	-1	1	2	4	12	13	15	17	19	22	29	33	43	47	57	61	71	73	75	77	80	85	86	88	90	93	99	113	127	142	155
Visit Windows											± 1 day																		± 3 days			
In house residency[a]		X	X	X																												
Informed consent	X																															
Medical history	X																															
Demographics	X																															
Physical examination	X	X	X[b]			X		X[b]				X		X		X		X					X						X			X
C-SSRS + PHQ-9	X	X										X																	X			X
Body weight	X		X[b]			X		X[b]				X		X		X		X					X						X			X
Height	X																															
Body Mass Index	X																															
Waist Circumference			X[b]					X[b]				X		X		X		X					X						X			X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X	X	X	X	X[b]				X		X		X		X					X						X			X
12-Lead ECG[c]	X	X	X[b,d]			X		X[b]				X		X		X		X					X									X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]			X		X[b]				X		X		X		X					X						X			X
Clinical Hematology[e]	X	X	X[b]			X		X[b]				X		X		X		X					X						X			X
Coagulation Tests[e]	X																															

Footnotes defined on next page of the table

Table 1-9. Schedule of Activities for Q2W Dose Titration – Cohort 6c

	Screening	Treatment																										Follow-up			EOS
Study Day	-28	-1	1	2	4	12	13	15	17	19	22	29	33	43	47	57	61	71	73	75	77	80	85	86	88	90	93	99	113	127	142	155
Visit Windows											± 1 day																		± 3 days			
eGFR[e]	X	X																														
Urinalysis[e]	X																															
Alcohol, Cotinine, and Drug Screen[e]	X																															
HIV, HBcAb, HBsAg, and HepCAb[e]	X																															
Pregnancy Test[h,j]	X	X[i]																														
Serum FSH Test (Females Only)[k]	X																															
DOSING																																
Study Drug Administration (SC)			X					X				X		X		X		X					X									
BLOOD SAMPLES (± WINDOW)																																
Serum PK[f]			X[b]		X			X[b]		X		X[b]	X	X[b]	X	X[b]	X	X[b]	X	X	X	X	X[b]	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]					X[b]				X				X							X						X			X
Serum PD (FFA)[f,g]			X[b]					X[b]				X				X							X						X			X
Serum endogenous GDF15[f,g]			X[b]					X[b]				X				X							X						X			X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]					X[b]				X				X							X						X			X
HbA1c[l]	X											X				X							X						X			X
Pharmacogenetic			X[b]																													
Biomarker Development[g]			X[b]					X[b]			X																			X			X
Anti-AMG 171 antibody[m]			X[b]					X[b]				X[b]																		X			X

ADA = anti-drug antibody; BP = blood pressure; CSSR-S = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = epidermal growth factor receptor; EOS = end of study; FFA = free fatty acid; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1C; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HDL-C = high-density lipoprotein cholesterol; HepCAb = hepatitis C antibody; HIV = human immunodeficiency virus; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic(s); PHQ-9 = 9 question Patient Health Questionnaire; PK = pharmacokinetic(s); Q2W = every 2 weeks; SC = subcutaneous; TEMP = temperature.

[a] In house residency day -1 to day 2

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 predose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by principal investigator

[g] 10-hour fasting is required at all timepoints.

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH Test (female only) for postmenopausal status confirmation

[l] Local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

Table 1-10. Schedule of Activities for Q1W Dose Titration – Cohort 7a

	Screening	Treatment																																				Follow-up			EOS
Study Day	-28	-1	1	2	4	5	6	7	8	9	10	11	12	14	15	17	18	22	24	25	29	30	36	40	44	50	51	54	56	59	64	78	79	81	83	86	92	106	120	134	148
Visit Windows																		± 1 day																				± 3 days			
In house residency[a]		X	X	X																																					
Informed consent	X																																								
Medical history	X																																								
Demographics	X																																								
Physical examination	X	X	X[b]			X			X[b]				X		X			X					X			X					X	X						X			X
C-SSRS + PHQ-9	X	X																																							X
Body weight	X		X[b]			X			X[b]				X		X			X					X			X					X	X						X			X
Height	X																																								
Body Mass Index	X																																								
Waist Circumference			X[b]						X[b]						X			X				X	X			X					X	X						X			X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X	X	X	X		X[b]	X		X	X	X	X			X				X	X			X					X	X						X			X
12-Lead ECG[c]	X	X	X[b,d]			X			X[b]				X		X			X				X	X			X					X	X									X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]			X			X[b]						X			X				X	X			X					X	X						X			X
Clinical Hematology[e]	X	X	X[b]			X			X[b]						X			X				X	X			X					X	X						X			X
Coagulation Tests[e]	X																																								

Footnotes defined on next page of the table

Table 1-10. Schedule of Activities for Q1W Dose Titration – Cohort 7a

	Screening	Treatment																																						Follow-up			EOS
Study Day	-28	-1	1	2	4	5	6	7	8	9	10	11	12	14	15	17	18	22	24	25	29	30	36	40	44	50	51	54	56	59	64	78	79	81	83	86	92	106	120	134	148
Visit Windows																		± 1 day																				± 3 days			
eGFR[e]	X	X																																							
Urinalysis[e]	X																																							
Alcohol, Cotinine, and Drug Screen[e]	X																																							
HIV, HBcAb, HBsAg, and HepCAb[e]	X																																							
Pregnancy Test[h,j]	X	X[i]																																						
Serum FSH Test (Females Only)[k]	X																																							
DOSING																																								
Study Drug Administration (SC)			X						X						X			X					X			X					X	X									
BLOOD SAMPLES (± WINDOW)																																								
Serum PK[f]			X[b]		X				X[b]			X			X[b]		X	X[b]		X			X[b]	X		X[b]	X	X		X	X[b]	X[b]	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]						X[b]									X								X						X						X			X
Serum PD (FFA)[f,g]			X[b]						X[b]									X								X						X						X			X
Serum endogenous GDF15[f,g]			X[b]						X[b]									X								X						X						X			X
Lipid Panel (total cholesterol, LDL-C, HDL-C, and triglycerides[g,l]	X		X[b]						X[b]									X								X						X						X			X

Footnotes defined on next page of the table

Table 1-10. Schedule of Activities for Q1W Dose Titration – Cohort 7a

	Screening	Treatment																																				Follow-up			EOS
Study Day	-28	-1	1	2	4	5	6	7	8	9	10	11	12	14	15	17	18	22	24	25	29	30	36	40	44	50	51	54	56	59	64	78	79	81	83	86	92	106	120	134	148
Visit Windows																		± 1 day																				± 3 days			
HbA1c[l]	X																	X								X						X						X			X
Pharmacogenetic			X[b]																																						
Biomarker Development[g]			X[b]						X[b]									X																					X		X	
Anti-AMG 171 antibody[m]			X[b]												X[b]								X[b]																X			X

ADA = anti-drug antibody; BP = blood pressure; CSSR-S = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = epidermal growth factor receptor; EOS = end of study; FFA = free fatty acid; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1C; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HDL-C = high-density lipoprotein cholesterol; HepCAb = hepatitis C antibody; HIV = human immunodeficiency virus; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic(s); PHQ-9 = 9 question Patient Health Questionnaire; PK = pharmacokinetic(s); Q1W = weekly; SC = subcutaneous; TEMP = temperature.

[a] In house residency day -1 to day 2

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 predose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by principal investigator

[g] 10-hour fasting is required at all timepoints.

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH Test (female only) for postmenopausal status confirmation

[l] Local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

Table 1-11. Schedule of Activities for Q1W Dose Titration – Cohort 7b

	Screening	Treatment																																							Follow-up			EOS
Study Day	-28	-1	1	2	4	5	6	7	8	9	10	11	12	14	15	18	19	21	22	25	26	28	30	36	40	44	50	54	58	64	67	68	70	73	78	79	81	83	86	92	106	120	134	148
Visit Windows																			± 1 day																						± 3 days			
In house residency[a]		X	X	X																																							
Informed consent	X																																										
Medical history	X																																										
Demographics	X																																										
Physical examination	X	X	X[b]			X			X[b]				X		X				X					X			X			X				X							X			X
C-SSRS + PHQ-9	X	X																																										X
Body weight	X		X[b]			X			X[b]				X		X				X					X			X			X				X							X			X
Height	X																																										
Body Mass Index	X																																										
Waist Circumference			X[b]						X[b]						X				X				X	X			X			X				X							X			X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X	X	X	X		X[b]	X		X	X	X	X				X				X	X			X			X				X							X			X
12-Lead ECG[c]	X	X	X[b,d]			X			X[b]				X		X				X				X	X			X			X				X										X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]			X			X[b]						X				X				X	X			X			X				X							X			X
Clinical Hematology[e]	X	X	X[b]			X			X[b]						X				X				X	X			X			X				X							X			X
Coagulation Tests[e]	X																																										
eGFR[e]	X	X																																									

Footnotes defined on next page of the table

Table 1-11. Schedule of Activities for Q1W Dose Titration – Cohort 7b

	Screening	Treatment																																					Follow-up			EOS
Study Day	-28	-1	1	2	4	5	6	7	8	9	10	11	12	14	15	18	19	21	22	25	26	28	30	36	40	44	50	54	58	64	67	68	70	73	78	79	81	83	86	92	106	120	134	148
Visit Windows																			± 1 day																					± 3 days			
Urinalysis[e]	X																																										
Alcohol, Cotinine, and Drug Screen[e]	X																																										
HIV, HBcAb, HBsAg, and HepCAb[e]	X																																										
Pregnancy Test[h,j]	X	X[i]																																									
Serum FSH Test (Females Only)[k]	X																																										
DOSING																																											
Study Drug Administration (SC)			X						X						X				X					X			X			X					X								
BLOOD SAMPLES (± WINDOW)																																											
Serum PK[f]			X[b]		X				X[b]				X		X[b]		X		X[b]			X		X[b]		X	X[b]		X	X[b]		X	X	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]						X[b]										X								X							X					X			X
Serum PD (FFA)[f,g]			X[b]						X[b]										X								X							X					X			X
Serum endogenous GDF15[f,g]			X[b]						X[b]										X								X							X					X			X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]						X[b]										X								X							X					X			X
HbA1c[l]	X																		X								X							X					X			X
Pharmacogenetic			X[b]																																								
Biomarker Development[g]			X[b]						X[b]										X																					X		X	
Anti-AMG 171 antibody[m]			X[b]												X[b]									X[b]																X			X

ADA = anti-drug antibody; BP = blood pressure; CSSR-S = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = epidermal growth factor receptor; EOS = end of study; FFA = free fatty acid; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1C; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HDL-C = high-density lipoprotein cholesterol; HepCAb = hepatitis C antibody; HIV = human immunodeficiency virus; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic(s); PHQ-9 = 9 question Patient Health Questionnaire; PK = pharmacokinetic(s); Q1W = weekly; SC = subcutaneous; TEMP = temperature.

[a] In house residency day -1 to day 2

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 predose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by principal investigator

[g] 10-hour fasting is required at all timepoints.

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH Test (female only) for postmenopausal status confirmation

[l] Local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

Table 1-12. Schedule of Activities for Q1W Dose Titration – Cohort 7c

	Screening	Treatment																																						Follow-up			EOS
Study Day	-28	-1	1	2	4	5	6	7	8	9	10	11	12	14	15	18	19	21	22	25	26	28	30	36	40	44	50	54	58	64	67	68	70	73	78	79	81	83	86	92	106	120	134	148
Visit Windows																			± 1 day																						± 3 days			
In house residency[a]		X	X	X																																								
Informed consent	X																																											
Medical history	X																																											
Demographics	X																																											
Physical examination	X	X	X[b]			X			X[b]				X		X				X					X			X			X					X						X			X
C-SSRS + PHQ-9	X	X																																										X
Body weight	X		X[b]			X			X[b]				X		X				X					X			X			X					X						X			X
Height	X																																											
Body Mass Index	X																																											
Waist Circumference			X[b]						X[b]						X				X				X	X			X			X					X						X			X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[b]	X	X	X	X		X[b]	X		X	X	X	X				X				X	X			X			X					X						X			X
12-Lead ECG[c]	X	X	X[b,d]			X			X[b]				X		X				X				X	X			X			X					X									X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e,g]	X	X	X[b]			X			X[b]						X				X				X	X			X			X					X						X			X
Clinical Hematology[e]	X	X	X[b]			X			X[b]						X				X				X	X			X			X					X						X			X
Coagulation Tests[e]	X																																											
eGFR[e]	X	X																																										

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Table 1-12. Schedule of Activities for Q1W Dose Titration – Cohort 7c

	Screening	Treatment																																					Follow-up			EOS
Study Day	-28	-1	1	2	4	5	6	7	8	9	10	11	12	14	15	18	19	21	22	25	26	28	30	36	40	44	50	54	58	64	67	68	70	73	78	79	81	83	86	92	106	120	134	148
Visit Windows																			± 1 day																						± 3 days			
Urinalysis[e]	X																																										
Alcohol, Cotinine, and Drug Screen[e]	X																																									
HIV, HBcAb, HBsAg, and HepCAb[e]	X																																									
Pregnancy Test[h,j]	X	X[i]																																								
Serum FSH Test (Females Only)[k]	X																																									
DOSING																																										
Study Drug Administration (SC)			X						X						X				X					X			X					X										
BLOOD SAMPLES (± WINDOW)																																										
Serum PK[f]			X[b]		X				X[b]				X		X[b]		X		X[b]	X				X[b]	X		X[b]	X		X[b]				X[b]	X	X	X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, Glucagon)[f,g]			X[b]						X[b]										X								X								X						X			X
Serum PD (FFA)[f,g]			X[b]						X[b]										X								X								X						X			X
Serum endogenous GDF15[f,g]			X[b]						X[b]										X								X								X						X			X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides[g,l]	X		X[b]						X[b]										X								X								X						X			X
HbA1c[l]	X																		X								X								X						X			X
Pharmacogenetic			X[b]																																									
Biomarker Development[g]			X[b]						X[b]										X																								X		X	
Anti-AMG 171 antibody[m]			X[b]												X[b]									X[b]																		X			X

ADA = anti-drug antibody; BP = blood pressure; CSSR-S = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = epidermal growth factor receptor; EOS = end of study; FFA = free fatty acid; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1C; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HDL-C = high-density lipoprotein cholesterol; HepCAb = hepatitis C antibody; HIV = human immunodeficiency virus; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; PD = pharmacodynamic(s); PHQ-9 = 9 question Patient Health Questionnaire; PK = pharmacokinetic(s); Q1W = weekly; SC = subcutaneous; TEMP = temperature.

[a] In house residency day -1 to day 2

[b] Predose assessments

[c] Single ECG during screening (day -28 to day -1) and triplicate at other timepoints unless otherwise specified. 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)

[d] 3 sets of triplicate ECGs at baseline (day 1 predose)

[e] Analyzed at the local laboratory, additional samples may be collected for safety reasons as defined by principal investigator

[f] Analyzed at the central laboratory/sponsor facility, additional samples may be collected for safety reasons as defined by principal investigator

[g] 10-hour fasting is required at all timepoints.

[h] Serum pregnancy test at screening and EOS (females only)

[i] Urine pregnancy test (females only)

[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] Serum FSH Test (female only) for postmenopausal status confirmation

[l] Local laboratory at screening, then central laboratory at other timepoints

[m] All ADA samples will be taken prior to dosing on days of dose administration

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 significant side effects. AMG 171 is a long acting Fc fusion protein of Growth Differentiation Factor 15 (GDF15). In preclinical studies AMG 171 administration in obese cynomolgus monkeys resulted in an approximate 12% reduction in body weight as compared to 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 and multiple ascending doses of AMG 171 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 health-care 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 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 (NASH), 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 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: **glucagon-like peptide (**GLP**)**-1R agonists (liraglutide [Saxenda®]) **and semaglutide [Wegovy®]**, 5-HTR agonists (lorcaserin [Belviq®]), 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 2–9 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 (44-75%) 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 lorcaserin, 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 171

2.2.2.1 Pharmacology

AMG 171 is a recombinant growth differentiation factor 15 (GDF15) fragment crystallizable (Fc) fusion protein intended for the treatment of obesity. GDF15 is a distant member of the transforming growth factor-β (TGFβ) superfamily which has been associated with multiple disorders of metabolism such as obesity and insulin resistance (Breit et al, 2017). It is found in the circulation as a 25 kilodalton (KD) homodimer protein. Literature findings support GDF15 as a potential regulator of body weight and fat mass. Genetically engineered mice which do not express GDF15 have increased body weight, where overexpression resulted in mice with lower body weight and fat mass (Tsai et al, 2013; Johnen et al, 2007). Engineered GDF15 peptides administered to both mice and cynomolgus monkeys also resulted in lower body weight and fat mass (Xiong et al, 2017). GDNF family receptor α-like (GFRAL) has recently been identified as the hindbrain localized receptor that mediates GDF15 action (Yang et al, 2017; Emmerson et al, 2017; Mullican et al, 2017; Hsu et al, 2017). GFRAL associates with a coreceptor, rearranged during transfection (RET), that results in downstream

phosphorylation of effectors such as extracellular signal -related kinase (ERK) and protein kinase B (AKT). AMG 171 incorporates 1 Fc dimer per GDF15 subunit; this modification increases the half-life of GDF15 in the circulation. Binding affinity of AMG 171 to human, cynomolgus monkey, and mouse GFRAL was determined by measuring the binding kinetics of AMG 171 to a soluble form of human, cynomolgus monkey, or mouse GFRAL and then calculating affinity. AMG 171 binds to human, cynomolgus monkey, and mouse GFRAL with affinities of 1.8 $\pm$ 0.06 nM, 1.6 $\pm$ 0.3 nM, and 5.6 $\pm$ 0.4 nM, respectively.

In human embryonic kidney cells (HEK) 293T transiently expressing human, mouse, or cynomolgus monkey GFRAL and RET, AMG 171 increased measurable phosphorylated ERK with a mean half maximal effective concentration (EC_{50}) of 0.343 nM, 0.103 nM, and 0.356 nM respectively.

The effects of AMG 171 were examined in leptin deficient (ob/ob) and diet-induced obese mice (DIO) as well as spontaneously obese cynomolgus monkeys. In ob/ob mice AMG 171 dose-dependently reduced food intake with an average 50% effective dose (ED_{50}) value of 11.3 $\pm$ 3.1 μg/kg and with maximum inhibition of 30.5% $\pm$ 3.7%.

After 5 weeks of treatment of vehicle or AMG 171 in diet induced obese (DIO) mice, and after removal of animals that were suspected of anti-drug antibody (ADA) formation, body weight percent change from baseline for AMG 171 group was -21.6% and when compared to the vehicle group, AMG 171 group showed a 30.1% lower body weight.

AMG 171 was evaluated in obese non-human primates using a chronic dosing regimen. AMG 171 reduced food intake, body weight, insulin and triglyceride levels in obese cynomolgus monkeys after 5 weeks of dosing with sustained effect on the weight loss during the washout phase, suggesting a strong potential as an anti-obesity therapeutic.

The digestive tract is important for nutrient absorption following food intake. It is also known that gastric motility mediated by smooth muscle peristalsis dictates the rate at which ingested food is emptied from the upper digestive tract. Gastric emptying rates can be determined by using techniques such as time mediated retention of phenol red in the stomach or appearance of orally administered acetaminophen in blood (Clark and Williams, 1971; Clements et al, 1978; Paixao et al, 2018). The latter can be used in the clinical setting to determine gastric emptying rates in humans (Paixao et al, 2018). Changes in gastric emptying rates mediated by AMG 171 can provide insight into its mechanism of action on body weight and food intake. The phenol

red data showed higher gastric retention of phenol red after GDF15 treatment, indicating delayed gastric emptying by GDF15. When GDF15 was injected 30 minutes before oral gavage, acetaminophen levels were lower in GDF15 treated group. Area under the curve (AUC) of the acetaminophen curve shows 21.7% reduction by GDF15 treatment.

Refer to the AMG 171 Investigator's Brochure (IB) for additional information related to the pharmacology, physical, chemical, and pharmaceutical properties and formulations of AMG 171.

2.2.2.2 Pharmacokinetics

2.2.2.2.1 Non-clinical Pharmacokinetics

Single-dose PK of AMG 171 were characterized following intravenous (IV) and subcutaneous (SC) administration to cynomolgus monkeys. Multiple dose toxicokinetics (TK) were characterized following SC dosing to mice and cynomolgus monkeys.

AMG 171 single-dose PK was characterized after IV or SC administration of AMG 171 to lean (non-obese) male cynomolgus monkeys at 2 dose levels [redacted] mg/kg) to cover a 10-fold range. AMG 171 PK was linear based on dose-proportional increases in exposure (maximum observed concentration [C_{max}] and area under the concentration-time curve from 0 to infinity [$AUC_{0\text{-}inf}$]). The terminal half-life ($t_{1/2,z}$) in monkeys ranged between 6.1 to 7.1 days. AMG 171 was absorbed upon SC administration to monkeys with absolute bioavailability of 79%.

The multi-dose TK of AMG 171 was characterized in CD-1 mice in an exploratory study with weekly (QW) SC doses of [redacted] mg/kg for 4 weeks. Exposure was approximately dose-proportional during the week 1 dosing interval, with no evidence of drug accumulation over 4 weeks dosing. There was no observed sex difference in AMG 171 TK exposure.

The TK of AMG 171 in CD-1 mice was characterized study after SC doses of [redacted] and [redacted] mg/kg administered every 2 weeks (Q2W) for fourteen weeks. AMG 171 exposure increased with dose. There were no observed differences in TK parameters estimates (C_{max} and AUC_{last}) between males and females during the week 1 interval. There was no AMG 171 accumulation observed at all dose levels after repeat administration.

The multi-dose TK of AMG 171 was characterized in lean (non-obese) female cynomolgus monkeys in an exploratory study with SC doses of [redacted] mg/kg QW over 4 weeks. Following multiple doses, exposure was dose-proportional up to [redacted] mg/kg, but exposure was greater than dose proportional doses of [redacted] mg/kg based

on C_{max} and AUC_{last}. AMG 171 drug accumulation was observed for individual monkeys in all groups (up to 1.8-fold) upon repeat administration.

The TK of AMG 171 in cynomolgus monkeys was characterized after SC doses of [redacted] mg/kg administered Q2W for fourteen weeks. AMG 171 exposure increased approximately proportional to dose. Moderate AMG 171 accumulation (up to 1.6-fold) was observed upon repeated administration. No difference in exposure was observed between males and females.

2.2.2.3 Toxicology

A comprehensive nonclinical toxicology program was conducted to support the SC administration of AMG 171 in the proposed clinical study for up to 3 months. The nonclinical safety assessment of AMG 171 consisted of 4-week exploratory and 14-week **Good Laboratory Practices** (GLP)**-compliant** toxicology studies in the mouse and cynomolgus monkey. In addition, a single dose GLP**-compliant** central nervous system/respiratory safety pharmacology study in the mouse found no AMG 171-related effects, and a single dose GLP**-compliant** cardiovascular safety pharmacology study in the telemetered cynomolgus monkey was conducted.

In the 14-week studies, SC administration (Q2W) of doses up to [redacted] mg/kg and [redacted] mg/kg were well tolerated in the mouse and cynomolgus monkey, respectively. Mice administered [redacted] mg/kg had AMG 171-related decreases in body weight gain, the intended pharmacologic activity. Decreased body weights, primarily because of widespread decreased body fat and decreased overall growth, were associated with secondary effects that are consistent with an adaptive response to decreased body weight gains due to food or caloric restriction in rodents (Levin **et al**, 1993). All changes attributed to the intended pharmacologic activity of AMG 171 and secondary metabolic consequences showed signs of recovery by the end of the 4-month recovery phase, except for decreased serum lipid levels in females at [redacted] mg/kg. Additionally, insulin and glucose were lower than control for males at [redacted] mg/kg at the end of the recovery phase, which was attributed to improved insulin sensitivity. AMG 171-related changes that were not clearly secondary to body weight reductions included a mild increase in platelets and a minimal increase in alkaline phosphatase at all dose levels. The minimal increase in alkaline phosphatase at [redacted] mg/kg persisted through the recovery period. The no observed adverse effect level (NOAEL) in mice was [redacted] mg/kg.

Cynomolgus monkeys given [redacted] mg/kg SC Q2W for 14 weeks had few changes attributed to AMG 171. Two out of 16 animals, including the largest female on study

(administered [redacted] mg/kg) and a high dose male, lost weight which was attributed to the expected pharmacology of AMG 171. Females at [redacted] mg/kg had minimal to mild decreases in globulins which fully reversed by the end of the 4-month recovery phase. Minimal to mild mononuclear cell infiltrates observed in several tissues at both dose levels were attributed to an immunogenic response to a foreign human biotherapeutic and not a direct AMG 171-related effect (Engelhardt, 2008, Naylor et al, 2019). After the 4-month recovery phase, this finding was considered fully or partially reversed in all tissues. The NOAEL was [redacted] mg/kg in cynomolgus monkeys.

The effects of AMG 171 on the cardiovascular system were assessed in a dedicated cardiovascular safety pharmacology study in telemetered male cynomolgus monkeys (Study 150667). Animals were administered [redacted] mg/kg AMG 171 on day 1 and evaluated for 24 hours on days 1 and 5. There were no AMG 171-related effects on ECG parameters, heart rate, arterial pulse pressure, respiration rate, or body temperature. At [redacted] mg/kg, there were slight, transient increases in systolic (up to +8 mmHg), diastolic (+4 mmHg) and mean arterial pressures (+6 mmHg) on day 1 (but not on day 5). The change at this dose was associated with a C_{max} value that is approximately 90X higher than the estimated C_{max} for the highest dose in the clinical trial [redacted] mg).

The highest planned dose in the clinical trial ([redacted] mg) is associated with predicted exposure multiples of 5- and 28-times relative to the AUC at NOAEL in mice and monkeys, respectively.

2.3 Benefit/Risk Assessment

The potential benefits of AMG 171 include anticipated weight loss and improved cardiovascular risk factors associated with weight loss. Potential risks of AMG 171, as anticipated from animal data and the literature, are described below in Section 2.3.2.

2.3.1 Key Benefits

The key anticipated benefits of AMG 171 include clinically meaningful weight loss and its associated benefits of improved cardiovascular health, glucose metabolism, and overall well-being.

2.3.2 Key Risks

Potential risks of AMG 171, 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 171 antibodies). Other potential risks include blood pressure

changes (as was observed in cynomolgus monkeys), and risks commonly associated with targeting obesity pathways.

Key risks detailed below:

1. Nausea/Vomiting

Nausea and vomiting are common adverse reactions for molecules targeting the obesity pathways. Mild to moderate, non-serious adverse events of nausea and vomiting have been observed in **cohorts 1 through 5** approximately 1 to 4 days after receiving Investigational Product. All events were self-resolved. Nausea and vomiting are considered identified risks with AMG 171. Subjects will be monitored for signs and symptoms of adverse events of nausea and vomiting throughout the study.

2. Increased Blood Pressure

In a cardiovascular safety pharmacology study in cynomolgus monkeys, there were higher systolic (up to + 8 mm Hg), diastolic (+ 4 mm Hg) and mean arterial pressures (+ 6 mm Hg) 24 hours post-dose at the highest dose tested [redacted] mg/kg, which is associated with a ~90X higher C_{max} than estimated from the [redacted] mg dose) and was not observed at the low dose of [redacted] mg/kg. The effect was transient and was not observed on day 5 in the presence of continued exposure. Subjects will have their vital signs, including blood pressure, monitored throughout the study. **No abnormal trends in vital signs were observed in clinical cohorts 1 through 5 in blinded review of data available at the DLRMs**.

3. Hypersensitivity Reactions

As with any biologic, administration of AMG 171 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 171 will be administered SC or IV by a qualified clinical research staff member. Subjects will be monitored for signs and symptoms of hypersensitivity reactions during and after AMG 171 administration, such as fever, chills, shaking, hypotension, wheezing, itching, nausea, and/or rash.

4. Immunogenicity

As with all biological products, there is a potential for the development of anti-AMG 171 antibodies. Additionally, there is a theoretical possibility that anti-drug antibodies may inhibit native GDF15. The potential effects of anti-AMG 171 antibodies on subjects who might develop them are not known, but reduced efficacy of AMG 171 is a possibility. Subjects will be monitored for potential effects of ADA that may include antibody mediated adverse events (AEs), 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 171 antibodies. Additional blood samples may be obtained to evaluate any ADA-mediated effects on safety, PK, and PD during the study.

5. Injection Site Reactions

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

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 AMG 171.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of AMG 171 as single or 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 PK of AMG 171 as single or multiple doses in subjects with obesity	• AMG 171 PK parameters including, but not limited to, maximum observed concentration (C_{max}), the time of maximum observed concentration (T_{max}), and area under the concentration time curve (AUC)

• To evaluate the immunogenicity of AMG 171	• Incidence of anti-AMG 171 antibody formation

Objectives	Endpoints
Exploratory	
• To characterize the PD effects of AMG 171 as single or multiple doses in subjects with obesity	• Changes in PD parameters:
○ To assess the effect of AMG 171 on fasting and post-prandial (Part A) metabolic parameters	○ Changes in the fasting and post-mixed meal challenge glucose, insulin, c-peptide, glucagon, and free fatty acid (FFA) concentrations
○ To assess the effect of AMG 171 on gastric emptying in the single ascending dose cohorts (Part A)	○ Gastric emptying as assessed by acetaminophen absorption kinetics (C_{max} and AUC)
○ To assess the effect of AMG 171 on fasting lipid levels	○ Changes in fasting lipid levels, including, but not limited to, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides
○ To assess the effect of AMG 171 on hemoglobin A1c (HbA1c) in the multiple dose cohorts (Part B)	○ Changes in HbA1c levels
○ To assess the effect of AMG 171 on potential biomarkers	○ Changes in potential biomarkers including, but not limited to, inflammatory and adipose tissue markers
○ To assess the effect of AMG 171 on endogenous GDF15 levels	○ Changes in endogenous GDF15 levels
○ To assess the effects of AMG 171 on body weight, waist circumference and body mass index (BMI)	○ Changes in body weight, waist circumference, and BMI
○ To assess the effect of AMG 171 on body composition in the multiple dose cohorts (Part B)	○ Changes in body composition as measured by whole body dual-energy x-ray absorptiometry (DXA)

4. Study Design

4.1 Overall Design

This is a phase 1, randomized, double-blind, placebo-controlled, single and multiple ascending dose study in adult subjects with obesity. The study will be conducted at approximately 3-4 sites in the United States. Additional sites may be added.
AMG 171 will be administered SC. Part A (completed) was a single ascending dose (SAD) phase; Part B is a multiple dose phase in 1 cohort; and Part C is a titration phase with step dosing for 2 to 3 doses total. **Part D will be a multiple ascending dose titration phase with step dosing ranging from 6 to 8 ascending doses.** The study consists of a total of **12** cohorts: 2 cohorts (Part A; SAD), 1 cohort (Part B), 3 cohorts (Part C; titration)**, and 6 cohorts (Part D; multiple ascending dose titration)**.

Potential subjects will be screened within 28 days before day 1 to assess their eligibility to enter the study. Subjects will be confined at the Clinical Research Unit (CRU) from Check-in (morning of **d**ay -1) through the morning of day 6 in Part A (SAD phase), from day -1 for a 7-day (6-night) residency period and re-admitted on day -13 for a second 7-day (6-night) residency period in Part B. Subjects in Part C (cohorts 3 to 5) will be admitted after confirmed eligibility on day -1. Cohort 3 subjects will be admitted after confirmed eligibility on day -1 for a 7-day (6-night) residency period and re-admitted on day 14 for a second 7-day (6-night) residency period. Cohort 4 subjects will be admitted after confirmed eligibility on day -1 for a 7-day (6-night) residency period, re-admitted on day 14 for a second 7-day (6-night) residency period, and re-admitted on day 28 for a third 7-day (6-night) residency period. Cohort 5 subjects will be admitted after confirmed eligibility on day -1 for a 14-day (13-night) residency period.

Cohort 6 subjects will be admitted after confirmed eligibility on day -1 for a 2-day (1-night) residency period, re-admitted on days 14 and 28 for a 3-day (2-night) residency period, re-admitted on day 42 for a 7-day (6-night) residency period, and re-admitted on days 56, 70, and 84 for a 2-day (1-night) residency period.

Cohort 7 subjects will be admitted after confirmed eligibility on day -1 for a 3-day (2-night) residency period, and re-admitted on days 35, 49, 63, and 77 for a 3-day (2-night) residency period.

Part A (SAD; completed)

Seventeen subjects were enrolled into 2 cohorts (1 subject was replaced). No additional cohorts are planned for Part A. In each cohort, 8 subjects were randomized to receive AMG 171 or placebo SC (cohorts 1 and 1b) in a 3:1 ratio as described in Table 1-1. For

each cohort, the first 2 subjects (sentinel pair) were randomized such that 1 subject received AMG 171 and 1 subject received placebo. The sentinel pair was observed for at least 24 hours before the remaining subjects in the cohort were dosed, as there were no safety or tolerability concerns as assessed by the Principal Investigator. Enrollment into the SAD cohorts was sequential. Subsequent cohorts were dosed after the dose regimen in the preceding cohort was recommended by the Dose Level Review Team (DLRT) to **have no safety signals observed** and **be** reasonably tolerated based on the safety and laboratory data through at least study day 15 for at least 7 out of 8 subjects dosed. The 2 SAD cohorts have completed dosing. Cohort 1 has reached study completion and cohort 1b has completed 3 months of follow-up. As tolerability was noted to worsen with the dose increase from [redacted] mg (cohort 1) to [redacted] mg (cohort 1b) with adverse events of nausea and vomiting, titration to and above those dose levels will be evaluated in Part B.

Part B (Multiple Ascending Dose [MAD])

Approximately 8 subjects will enroll into 1 cohort (cohort 2) where 8 subjects will be randomized to receive AMG 171 or placebo SC in a 3:1 ratio as described in Table 1-1.

Cohort 2: Study drug will be administered SC every Q2W for a total of six**,** [redacted] mg doses.

Part C (Titration)

Approximately 24 subjects will enroll into 1 of 3 cohorts (cohorts 3 to 5). In each cohort, 8 subjects will be randomized to receive AMG 171 or placebo SC in a 3:1 ratio as described in Table 1-1. Enrollment into cohort 3 will occur after DLRT recommendation based on safety and laboratory data through at least study day 22 of cohort 2 (Part B). Subsequently, both cohorts 4 and 5 will be dosed after the dose regimen in the cohort 3 has been recommended by the DLRT to **have no safety signals observed** and **be** reasonably tolerated based on safety and laboratory data through day 22 for at least 6 out of 8 subjects dosed **and cumulative data of all prior cohorts**.

Enrollment of dose cohorts is depicted in Figure 1-1. **No additional cohorts are planned for Part C.**

Cohort 3: Two doses of study drug will be administered SC Q2W apart with the first dose of [redacted] mg and second dose of [redacted] mg.

Cohort 4: Three doses of study drug will be administered SC Q2W apart with the first dose of [redacted] mg, second dose of [redacted] mg and third dose of [redacted] mg.

Cohort 5: Two doses of study drug will be administered SC **weekly (**Q1W**)** apart with the first dose of [redacted] mg and second dose of [redacted] mg.

Part D (MAD Titration)

Approximately 48 subjects will enroll into 1 of 6 cohorts (cohorts 6a-c and 7a-c). In each cohort, 8 subjects will be randomized to receive 6 to 8 consecutive doses of AMG 171 or placebo SC in a 3:1 ratio as described in Section 1.3. The cohorts in group 6 will begin with [redacted] mg with dose escalation every 2 weeks while those in group 7 will begin with [redacted] mg with dose escalation weekly until the fourth dose and then every other week thereafter. Enrollment into cohorts 6a and 7a will begin contemporaneously after a Dose Level Review Meeting (DLRM) of cohorts 4 and 5, which include review of cumulative data of all prior cohorts. Enrollment in cohorts 6b and 7b will occur after DLRT recommendation based on all safety and laboratory data through at least study day 43 of cohort 6a (Part D) and cumulative data of all prior cohorts. Subsequently, cohorts 6c and 7c will be dosed in parallel after the dose regimen in cohort 6b has been recommended by the DLRT to have no safety signals observed and be reasonably tolerated based on all safety and laboratory data through at least study day 57 for at least 6 out of 8 subjects dosed and cumulative data of all prior cohorts. Enrollment of dose cohorts is depicted in Figure 1-1.

- **Cohort 6a: Study drug will be administered SC Q2W for a total of 7 doses [redacted].**
- **Cohort 6b: Study drug will be administered SC Q2W for a total of 7 doses [redacted].**
- **Cohort 6c: Study drug will be administered SC Q2W for a total of 7 doses [redacted].**
- **Cohort 7a: Study drug will be administered SC Q1W for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].**
- **Cohort 7b: Study drug will be administered SC Q1W for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].**
- **Cohort 7c: Study drug will be administered SC Q1W for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].**

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 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

Approximately **96** subjects (8 subjects per cohort, cohorts 1, 1b, 2 to 5**, 6a-c, and 7a-c**) will be enrolled. Additional subjects may be enrolled if a DLRT recommendation is made to expand, repeat or add cohorts to the study.

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 3 to 4 investigative sites in U.S. 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 starting dose and exposure multiples for the doses proposed for Part **A**, SAD were calculated based on the NOAELs determined in the 14-week GLP repeat-dose mouse and cynomolgus monkey toxicology studies (Q2W dosing, Section 2.2.2.3) and the observed reduction in body weight in the chronic efficacy study in cynomolgus monkeys. **The planned cohorts in this amendment of the study consists of multiple-dose cohorts following a titration schema as presented in** Figure 1-1.

Previously, subjects in Part A received a single [redacted] mg SC dose (cohort 1) or [redacted] mg SC (cohort 1b). Events of nausea and vomiting were observed in the [redacted] mg SC single dose cohort, with fewer and milder events noted in the [redacted] mg SC single dose cohort. All observed events were of mild to moderate intensity. Nausea and vomiting are common adverse reactions for molecules targeting the obesity pathways that at times require titration to overcome tolerability, eg, GLP-1R agonists.

Following this, a multiple dose cohort (Part B) **consisting of multiple doses** of [redacted] mg Q2W x 6 **was evaluated (cohort 2). This was** followed by a series of titration cohorts (Part C) with dose escalation over 2 to 3 doses **(cohorts 3, 4, and 5). The objective of Part C was to evaluate titration to reach higher exposures and to use a dose escalation approach starting from a dose that was previously shown to be tolerable, that is, [redacted] mg and assessing if the events of nausea and/or vomiting were related to initial drug exposures and later decreases with increase in dose/exposures.**

Based on preclinical PK analysis, the predicted half-life is approximately 11 days and therefore a regimen administering AMG 171 doses every 2 weeks was

evaluated in cohorts 3 and 4 (Part C). A weekly regimen was also evaluated in cohort 5 (Part C) as an alternative regimen approach.

The rationale for dose and regimen selection for Part D is based on the available safety and tolerability data from cohorts 3, 4, and 5. The available PK data from the ongoing first-in-human (FIH) study cohorts 1 to 5 (Parts A, B, and C) and the NOAEL exposures **established based on 14-week GLP repeat-dose toxicology studies in mouse and cynomolgus monkeys also support the selection of doses and regimen to be evaluated in Part D. Preliminary review of the PK data in cohorts 1 to 5 demonstrated that AMG 171 serum** exposures **increase in an approximately dose-proportional manner based on C_{max} (AUC data pending), with a half-life of approximately 12 days.**

In cohorts 1 to 5, adverse events of nausea and vomiting occurred at doses of AMG 171 ranging from [redacted] mg to [redacted] mg SC, though these events were generally mild and resolved over time, including with repeated doses. The dosing schema proposed in cohorts 6a-c and 7a-c (Part D) will seek to define optimal dosing titration to minimize nausea and vomiting. The proposed regimens to be evaluated in Part D are Q2W regimens in cohorts 6a, 6b, and 6c, and regimens with Q1W dose escalation followed by Q2W dose escalation in cohorts 7a, 7b, and 7c. These 2 distinct dose escalation approaches will allow us to identify the escalation strategy that minimizes nausea and vomiting.

The proposed doses to be evaluated in Part D of amendment are not to exceed [redacted] mg in cohort 6a and 7a, [redacted] mg in cohorts 6b and 7b, and [redacted] mg in cohorts 6c and 7c. The predicted human exposure multiples **for AMG 171** following **the highest** dose of [redacted] mg **in cohort 6c (Q2W regimen**) are **approximately 169- and 112-fold for** C_{max} and AUC, respectively**,** based on NOAEL established in cynomolgus monkeys**, and 90- and 21-fold for C_{max} and AUC, respectively, based on NOAEL established in mice (refer to** Table 4-1).

The predicted human exposure multiples for AMG 171 following the highest dose of [redacted] mg in cohort 7c (regimen consisting of QW doses up to [redacted] mg and Q2W doses thereafter until the last dose) are approximately 217- and 149-fold for C_{max} and AUC, respectively, based on NOAEL established in cynomolgus monkeys, and 116- and 28-fold for C_{max} and AUC, respectively, based on NOAEL established in mice (refer to Table 4-2).

Table 4-1. Predicted Human Exposures and Associated Exposure Multiples Following the Last Proposed AMG 171 Doses – Cohorts 6a, 6b, and 6c

			Exposure Multiples Based on AUC_{ss} at the NOAEL[a]		Exposure Multiples Based on C_{max} at the NOAEL[a]	
Clinical Dose (mg)	Anticipated Human C_{max} (µg/mL)	Anticipated Human AUC (µg·hr/mL)[b]	Mouse 14-week	Monkey 14-week	Mouse 14-week	Monkey 14-week
SC						
[redacted]			68	368	300	563
			39	208	177	331
			21	112	90	169

AUC = area under the curve; AUC_{ss} = area under the curve at steady state; C_{max} = maximum concentration; GLP = glucagon-like peptide; NOAEL = no observed adverse effect level; Q2W = every 2 weeks; SC = subcutaneous.

[a] Based on 14-week mouse GLP toxicology study NOAEL dose = [redacted] mg/kg Q2W, C_{max} = [redacted] µg/mL and AUC_{ss} = [redacted] µg-hr/mL; and based on 14-week GLP toxicology study in cynomolgus monkeys NOAEL dose = [redacted] mg/kg Q2W, C_{max} = [redacted] µg/mL and AUC_{ss} = [redacted] µg-hr/mL.

[b] Predicted multiples rounded to integer.

Table 4-2. Predicted Human Exposures and Associated Exposure Multiples Following the Last Proposed AMG 171 Doses – Cohorts 7a, 7b, and 7c

			Exposure Multiples Based on AUC_{ss} at the NOAEL[a]		Exposure Multiples Based on C_{max} at the NOAEL[a]	
Clinical Dose (mg)	Anticipated Human C_{max} (µg/mL)	Anticipated Human AUC (µg·hr/mL)[b]	Mouse 14-week	Monkey 14-week	Mouse 14-week	Monkey 14-week
SC						
[redacted]			81	438	323	605
			43	230	193	362
			28	149	116	217

AUC = area under the curve; AUC_{ss} = area under the curve at steady state; C_{max} = maximum concentration; GLP = glucagon-like peptide; NOAEL = no observed adverse effect level; Q2W = every 2 weeks; SC = subcutaneous.

[a] Based on 14-week mouse GLP toxicology study NOAEL dose = [redacted] mg/kg Q2W, C_{max} = [redacted] µg/mL and AUC_{ss} = [redacted] µg-hr/mL; and based on 14-week GLP toxicology study in cynomolgus monkeys NOAEL dose = [redacted] mg/kg Q2W, C_{max} = [redacted] µg/mL and AUC_{ss} = [redacted] µg-hr/mL.

[b] Predicted multiples rounded to integer.

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is the date when the last subject has completed the assessments for EOS.

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 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 120 days for Part A, 207 days for Part B, 85 days for cohorts 3 and 5, 113 days for cohort 4 (Part C)**, 155 days for cohort 6 (Part D), and 148 days for cohort 7 (Part D)**.

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 after signing the informed consent including limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during 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 prior to initiation of any study specific activities/procedures

102 Males and females age ≥ 18 to ≤ 65 years of age, 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 (Part A) and day -1 (Parts B and C) and screening

104 Body mass index (BMI) between ≥ 30.0 kg/m^2 and ≤ 40.0 kg/m^2

105 Have a stable body weight (less than 5 kg self-reported change during the previous 8 weeks) prior to 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 non-reproductive 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 Males must agree to practice an acceptable method of effective birth control while on study through 2 and half months after receiving the last dose of study drug. Acceptable methods of effective birth control include sexual abstinence; vasectomy and testing that shows there are no sperm in the semen; or a condom with spermicide (males) in combination with barrier methods (diaphragm, cervical cap or cervical sponge), hormonal birth control or IUD (females).

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 Hepatic liver enzymes ALT, AST, alkaline phosphatase (ALP), or total bilirubin (TBIL) levels > 1.5 times the upper limit of normal (ULN) at screening

204 History or clinical evidence of bleeding diathesis or any coagulation disorder, including prothrombin time (PT), activated partial thromboplastin time (APTT), International normalized ratio (INR) or platelet count outside of the laboratory's normal reference range at screening

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

206 Allergy or sensitivity to acetaminophen (for subjects in Part A)

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

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

209 Subjects with a history of renal impairment or renal disease and/or estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2

210 Obesity induced by other endocrinologic disorders (eg Cushing's Syndrome)

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

212 History of major depressive disorder

213 History of other severe psychiatric disorders, eg schizophrenia, bipolar disorder

214 A patient health questionnaire (PHQ-9) score of ≥ 10

216 Any suicidal ideation as identified by endorsement of (answered yes to) any of the items numbered 1-5 on the Columbia Suicide Severity Rating Scale (C-SSRS)

217 Surgery scheduled for the trial duration period, except for minor surgical procedures, at the discretion of the investigator

218 Positive results for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus ribonucleic acid (RNA). For hepatitis C, hepatitis C antibody (HepCAb) testing is done at screening, followed by hepatitis C virus RNA by polymerase chain reaction (PCR) if hepatitis C antibody is positive.

219 Subject has systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 90 mm Hg at screening, or on day -2 (Part A) or day -1 (Parts B and C). 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.

220 History of malignancy of any type, other than in situ cervical cancer or surgically excised non-melanomatous skin cancers occurring more than 5 years prior to randomization

Prior/Concomitant Therapy

221 Use of the following agents are excluded unless there is a prior consultation between the Principal 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 to acetaminophen up to 2 g per day for analgesia, and hormone replacement therapy (eg, estrogen, thyroid)
- All herbal medicines, vitamins, and supplements within 30 days prior to 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.

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

223 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 trial)

Prior/Concurrent Clinical Study Experience

224 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 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 2 and half a months after the last dose of AMG 171

227 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 2 and a half months after the last dose of AMG 171

228 Subject has known sensitivity to AMG 171 or components thereof or a history of drug or other allergy that is in the opinion of the investigator or medical monitor (if appropriate), contraindicates their participation

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

230 Subject has known sensitivity to mammalian derived products

231 Subject has a 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 Medical Monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

232 Subject is unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol is prohibited 48 hours prior to day -2 (Part A) and day -1 (Parts B and C) 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).

233 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.

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

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

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

237 Subject has donated or lost ≥ 500 mL of blood or plasma within 60 days of day -2 (Part A) and day -1 (Parts B and C)

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Subjects will be required to fast overnight for at least 10 hours prior to all blood draws for routine clinical laboratory, lipid profile and PD assessments 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 prior to admission to the research facility on day -2 (Part A) and day -1 (Parts B and C). 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 non-tobacco using subjects should be enrolled. Subjects should not have used any nicotine or tobacco containing products within the last 6 months prior to 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 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 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 informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned via IRT (see Section 6.4). 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 1 time after discussion with Amgen Medical Monitor. Refer to Section 8.1.1.

5.6 Washout Period/Run-in Period/Invasive Procedure(s)

This section is not applicable.

6. Treatments

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

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

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

6.1 Treatment(s) Administered

6.1.1 Investigational Products

Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] AMG 171	Placebo
Dosage Formulation	Colorless to slightly yellow liquid drug product in a [redacted]mL glass vial (12 vials per box) filled with a [redacted] mL deliverable volume of [redacted]mg/mL. The specific packaging dimensions are 8.9 x 6.7 x 4.5 cm.	Placebo will be presented in identical containers, and stored/packaged the same as AMG 171
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Refer to Table 1-1	
Route of Administration	SC injection	
Accountability	The unblinded pharmacist must provide AMG 171 or placebo from the Amgen supplied stock according to the IRT assignment. The, dose, start date/time, and lot number (after study is unblinded) of AMG 171 is to be recorded on each subject's CRF(s).	
Dosing Instructions	Administration of AMG 171 or placebo requires specific training which must be completed and documented prior to undertaking any administration related activities. AMG 171 will be delivered as 1+ injections SC. Dosing instructions are provided in the **modular** IPIM.	

IV = intravenous; SC = subcutaneous
[a] AMG 171 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Medical Devices

This section is not applicable.

6.1.3 Other Protocol-required Therapies

All other protocol-required therapies, including acetaminophen, 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 and 1b, will undergo a Gastric Emptying test after an overnight fast of a minimum of 10 hours. For this assessment, oral liquid acetaminophen 1000 mg (acetaminophen Extra Strength) is administered followed immediately by administering a standardized liquid meal (ie, 16 fl oz, or 2 bottles or

cans, of Ensure Plus®). Timing of PK samples of acetaminophen after the standardized meal are summarized in the Schedule of Activities in **Section 1.3**.

6.1.4 Other Treatment Procedures

This section is not applicable.

6.1.5 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug**, combination product,** or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors and 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 products provisioned and/or repackaged/modified by Amgen including AMG 171 and placebo.

Any product complaint(s) associated with investigational products supplied by Amgen are to be reported according to the instructions provided in the **modular** IPIM.

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

With exception to acetaminophen up to 2 g per day for analgesia and hormone replacement therapy (eg, estrogen, thyroid), use of any over-the-counter or prescription medications within the 14 days or 5 half-lives (whichever is longer) prior to dosing on day 1, and for the duration of the study, is not permitted unless to treat a medical emergency. For subjects in Part A, acetaminophen should not be consumed within 72 hours of the Gastric Emptying test, otherwise the same guidance applies. In addition, it is recommended that subjects avoid starting new or changing herbal medicines, vitamins and supplements unless reviewed and approved by the Principal Investigator and Amgen Medical Monitor within 30 days prior to dosing on day 1 and for the duration of the study. Any changes regarding concomitant medications should be recorded on the subject's source documents and the CRF along with the reason for the change.

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 tolerated based on available study data through study day 15 for all dosed subjects (cohorts 1 and 1b) or study day 22 for at least 6 of 8 dosed subjects (cohorts 2 and 3), as applicable and upon unanimous agreement of the DLRT members. **Enrollment into cohorts 6a and 7a will begin contemporaneously after a DLRM of cohorts 4 and 5, which include review of cumulative data of all prior cohorts. Enrollment in cohorts 6b and 7b will occur after DLRT recommendation based on all safety and laboratory data through at least study day 43 of cohort 6a (Part D) and cumulative data of all prior cohorts. Subsequently, cohorts 6c and 7c will be dosed in parallel after the dose regimen in cohort 6b has been recommended by the DLRT to have no safety signals observed and be reasonably tolerated based on all safety and laboratory data through at least study day 57 for at least 6 out of 8 subjects dosed and cumulative data of all prior cohorts.**

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. Further information on **DLRMs** is provided in 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 6-2 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 6-2.

Table 6-2. 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 AE 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 AE 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.

AE = adverse event; DLRM = dose level review meeting; DLRT = Dose Limiting Review Team; NIH = National Institutes of Health.
Adverse drug reaction = adverse events with causal association to the study drug per the investigator.
NIH nausea: grade 1 – transient (< 24 hours) or intermittent with no or minimal interference with normal intake; grade 2 – persistent nausea resulting in decreased oral intake for 24-48 hours; grade 3 – minimal oral intake for >48 hours or aggressive rehydration (intravenous fluids). NIH vomiting: grade 1 – transient or intermittent vomiting with no or minimal interference with normal intake; grade 2 – frequent episodes of vomiting with no or mild dehydration; grade 3 – persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (eg, intravenous fluids) (Sibille et al, 2010).
Please refer to Section 11.4 for additional information on adverse events and safety reporting.

[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 suspected adverse drug reactions, and serious adverse events 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 171

The reason for dose change of AMG 171/placebo is to be recorded on each subject's CRF(s). Refer to Section 11.3

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

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

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and other protocol-required therapies and during the study are provided in the **modular** 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 of AMG 171 to placebo for cohorts 1, 1b, 2 to 5, **6a-c, and 7a-c,** in a double-blind manner, respectively.

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 records and on the enrollment case report form (CRF).

6.4.2 Blinding

This is a double-blind study. 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 prior to the study being formally unblinded.

6.5 Treatment Compliance

Study drug will be administered at the clinic by qualified staff.

6.6 Treatment of Overdose

The effects of overdose of AMG 171 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 8.2.4.

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 prior to enrollment through the first dose of investigational product should 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 6.1.6.

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 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 below in Sections 7.1, 7.2, and 7.3.

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
- Protocol-specified criteria (eg meets hepatotoxicity stopping rules per Section 11.7 and/or Mental Health Criteria Stopping Rules Section 11.8)
- 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). Subject will be encouraged to attend a safety follow up visit to complete EOS assessment. Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether 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, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days/4 weeks.

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 re-screening 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/4 weeks 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 and Follow-up

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 pre-dose assessments and/or procedures during each visit that it is required.

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).

8.1.3 End of Study

End of Study (EOS) visit procedures will be performed per the Schedule of Activities (Section 1.3). For subject completing the study, this visit occurs on day 120 (Part A) or day 207 (Part B), a minimum of 70 days after the last scheduled dose (Part C)**, and a minimum of 60 days after the last scheduled dose (Part D)**. If feasible, all EOS procedures should be performed at the final visit for subjects who are removed from study prior to the defined EOS 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.

8.2.1 General Assessments

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 PK 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 electrocardiograms (ECGs), vital signs, 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:

For the SAD cohorts (Part A):

- ± 5 minutes window around the target completion time for tests and samples through 24 hours post-dose
- ± 1 hour on subsequent days in-house
- Per the visit windows through EOS

For the multiple dose and titration cohorts (Parts B**,** C**, and D**):

- Per the visit windows through EOS

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.

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. Pre-dose abnormal findings will be reported on the medical history page of the CRF.

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: BMI (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 or 1/2 inch 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, and drugs of abuse.

8.2.2 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 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 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. 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), prior to 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 pre-dose. The PI or (eg, designated site physician) will review all ECGs. 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 1.

8.2.2.3 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.2.2.4 Suicidal Risk Monitoring

AMG 171 is considered to be central nervous system (CNS)-active.

Subjects being treated with multiple doses of AMG 171 (Parts B**,** C**, and D**) must be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration is to be given to discontinuing AMG 171 in subjects who experience signs of suicidal ideation or behavior.

Families and caregivers of subjects being treated with multiple doses of AMG 171 are to be instructed to monitor subjects for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

For Parts B**, C, and D**, 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 Health Questionnaire 9 (PHQ-9). The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items. C-SSRS 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. Refer to Sections 11.8 through Section 11.10 for more information on mental health monitoring.

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 end of study are reported using the Event CRF.

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 end of study/safety follow-up visit are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's knowledge 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

If the investigator becomes aware of serious adverse events **suspected to be related to investigational product after** the protocol-required reporting period **(as defined in Section 8.2.3.1.2) is complete, then** these serious adverse events **will** be reported to Amgen within 24 hours following the investigator's knowledge of the event **on the Events CRF**.

If the study endpoint is overall survival, then the sites will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours of awareness.

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 if the subject ends the study.

8.2.3.1.4 Reporting a Safety Endpoint as a Study Endpoint

Not applicable

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 knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the 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 2 and half months after receiving last dose of study drug.

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.

8.2.3.7 Adverse Device Effects

This section is not applicable.

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 Event 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

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for all female subjects.

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.

For all female subjects, a serum pregnancy test should be performed according to the schedule of assessments including the EOS/safety follow up visit after discontinuing protocol-required therapies and 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 receive AMG 171 will have PK samples assessed.

Whole blood samples of approximately 5 mL will be collected for measurement of serum concentrations of AMG 171 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.

Blood samples (approximately 7 × 1 mL for acetaminophen PK, cohort 1 and 1b) 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 171 treatment PD effects at each time point specified in the Schedule of Activities.

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 171. Additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

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

8.2.8 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Section 1.3) for the measurement of anti-AMG 171 binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized. Additional blood samples may be obtained to rule out anti-AMG 171 antibodies during the study.

Sites will be notified of any positive neutralizing antibody results to AMG 171 for individual subjects at the end of the study for each subject. If results are not provided, no neutralizing antibodies to AMG 171 have been detected.

This notification is independent of and may be in advance of the time point when the entire study is planned to be unblinded. Refer to Section 6.4.2 for additional information regarding unblinding.

Subjects who test positive for neutralizing antibodies to AMG 171 at the final scheduled study visit defined as the end of study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result until: (1) neutralizing antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of AMG 171. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive AMG 171.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-AMG 171 antibody response may also be asked to return for additional follow-up testing. Refer to the Schedule of Activities (**Section 1.3**), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.

8.2.9 Biomarker Discovery

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

Samples will also be collected for biomarker analysis, eg, to evaluate potential biomarkers that may correlate with treatment response.

Blood will be collected for biomarker discovery at the time points specified in the Schedule of Activities (Section 1.3). Plasma and/or serum may also be used for DNA, RNA, and protein expression analysis including somatic mutations in order to correlate levels of expression with response.

8.2.9.1 Biomarker Development/Future Research

Biomarker Development refers to using samples collected for Biomarker Discovery for future research after the study ends.

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

If consent is provided by subjects, biomarker discovery samples collected at the time points specified in the Schedule of Activities will be retained for future biomarker development as described in Section 11.6. No additional samples will be collected for biomarker development/future research.

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 171 to investigate and further understand obesity and /or metabolic conditions.

8.2.10 Health Economics

This section is not applicable.

8.2.11 Other Assessments

Dual-energy x-ray absorptiometry (DXA)

Dual-energy x-ray absorptiometry (DXA) scans of body composition [eg, fat, muscle and bone mineral content (BMC)] will be conducted in cohort 2 as outlined in the Schedule of Activities (Section 1.3). The central vendor will provide an instructional manual.

Gastric Emptying Test

Subject in cohorts 1 and 1b, underwent a Gastric Emptying test as measured by acetaminophen absorption and PK on day -1, and day 5. The gastric emptying test

(initiated early in the morning) was performed after an overnight fast for at least 10 hours. Subjects received 1000 mg of oral liquid acetaminophen (Major®Extra Strength), followed immediately by a standardized meal (ie, bottles or cans, of Ensure Plus®). Subjects were allowed to take up to 10 minutes to consume the standardized meal. As part of this evaluation, multiple blood samples were collected for acetaminophen PK to measure gastric emptying, as well as PD measurements, per the Schedule of Activities (Section 1.3).

Please refer to the central laboratory manual for instructions on the collection of these samples.

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 hypothesis will be tested. For safety considerations, with up to **72** subjects (12 subjects from Part A, 6 subjects in Part B, 18 subjects from Part C**, and 36 subjects from Part D**) receiving AMG 171, the chance of detecting an adverse event with a true incidence rate of **2**% or greater is larger than **77**% and the chance of detecting an adverse event with a true incidence rate of **4**% or greater is larger than **95**%.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

9.3.1.1 Safety Analysis Set

The safety analysis set will consist of all subjects who receive at least 1 dose of investigational product on day 1.

9.3.1.2 Pharmacokinetic (PK) Analysis Set

The PK analysis set will consist of all subjects who received at least 1 dose of AMG 171 for whom at least 1 PK parameter or endpoint can be adequately estimated.

9.3.1.3 Pharmacodynamic (PD) Analysis Set

The PD analysis set will consist of all subjects who received 1 dose of investigational product for whom at least 1 PD 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 following 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

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.

9.4.1.2 Primary Analysis

The primary analysis will occur after all subjects have completed the study. Data will be locked prior to the primary analysis and a clean snapshot of the data will be used for the primary analysis.

9.4.1.3 Final Analysis

The primary analysis will be the final analysis for this study.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK and PD endpoints. 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. Data will be presented and summarized by treatment and at each time point. Graphical summaries of the data may also be presented.

Data for subjects receiving placebo may be combined across cohorts within Parts A, B, and C.

Data for subjects receiving AMG171 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

This section is not applicable.

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, and adverse events leading to withdrawal from investigational product or other protocol-required therapies. The number and percentage of subjects reporting adverse events will be evaluated for each dose cohort, across dose cohorts. Adverse events resulting in treatment discontinuation will be identified. Subject incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

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 (QTcF) will be categorized, and the number and percentage of subjects in each group will be summarized. Subjects' maximum post-baseline 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 plotted.

9.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 171 antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

9.4.2.3.8 Exposure to Investigational Product

The number of doses of IP 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 Non-investigational Product

Not applicable

9.4.2.3.10 Exposure to Other Protocol-required Therapy

Not applicable.

9.4.2.3.11 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

Serum AMG 171 concentrations will be determined using a validated assay. Individual serum concentration-time plots for AMG 171 will be presented for each subject as well as mean concentration-time plots for each dose cohort. PK parameters that may include, but are not limited to AUC, C_{max}, and T_{max} will be estimated using either compartmental (eg, PK modeling) or non-compartmental methods. Actual dosing and

sampling times will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter for each dose cohort.

Plasma acetaminophen concentrations as part of the Gastric Emptying 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 $AUC_{0\text{-}5h}$ as well as maximum plasma acetaminophen concentrations (C_{max}), and time of C_{max} (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. The safety analysis set will be used for all exploratory endpoint analysis performed.

10. References

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ADA	**anti-drug antibody**
AUC	**area under the curve**
CFR	U.S. Code of Federal Regulations
C_{max}	**maximum observed concentration**
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DES	Amgen data element standard
DILI	drug induced liver injury
DLRM	Dose level review meeting
DLRT	Dose Level Review Team
ECG	electrocardiogram
EDC	electronic data capture
eGFR	**epidermal growth factor receptor**
Enrollment	defined as when the investigator decides that the subject has met all eligibility criteria and assigns a randomization number
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
EOS	**end of study**
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
End of Study (end of trial)	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), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
FFA	**free fatty acid**
FIH	**first-in-human**
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	**Good Laboratory Practice**
GLP1R	**glucagon-like peptide-1 receptor**
HBcAb	**hepatitis B core antibody**

Abbreviation or Term	Definition/Explanation
HBsAg	**hepatitis B surface antigen**
HDL-C	**high-density lipoprotein cholesterol**
HepCAb	**hepatitis C antibody**
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
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
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
LDL-C	**low-density lipoprotein cholesterol**
MAD	**multiple ascending dose**
NCT	National Clinical Trials
NOAEL	**no observed adverse effect level**
PHQ-9	Patient Health Questionnaire 9
PD	**pharmacodynamic(s)**
PK	**pharmacokinetic(s)**
Q1W	**weekly**
Q2W	**every 2 weeks**
Randomization	defined as once a unique subject randomization number has been assigned via IRT at enrollment
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 trial necessary for the reconstruction and evaluation of the trial. 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.
Study day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
SUSAR	suspected unexpected serious adverse reaction

Abbreviation or Term	Definition/Explanation
TMF	trial master file
ULN	upper limit of normal

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the central laboratory and/or by the local laboratory as described in Section 1.3. **Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).**

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

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

Table 11-1. Analyte Listing

Local Laboratory: **Chemistry**	Local Laboratory: **Coagulation**	Local Laboratory: **Urinalysis**	Local Laboratory: **Hematology**	**Other**
Sodium	PT/INR	Specific gravity	RBC	**Local Laboratory**:
Potassium	APTT	pH	Nucleated RBC	Pregnancy (Serum or Urine)
Chloride		Blood	Hemoglobin	Hep B surface antigen
Bicarbonate		Protein	Hematocrit	Hep C antibody
Total protein		Glucose	MCV	HIV[a]
Albumin		Bilirubin	MCH	FSH
Calcium		WBC	MCHC	TSH
Magnesium		RBC	RDW	Lipid panel[b]
Phosphorus		Epithelial cells	Reticulocytes	• HDL
Glucose		Bacteria	Platelets	• LDL
BUN or Urea		Casts	WBC Differential	• Triglycerides
Creatinine		Crystals	• Bands/stabs	• Cholesterol
Uric acid			• Segmented Neutrophils	HbA1c[b]
Creatine kinase			• Eosinophils	**Central Laboratory**:
Total bilirubin			• Basophils	Antibodies
Direct bilirubin			• Lymphocytes	Serum PK
ALP			• Monocytes	Plasma PD:
LDH			• Total Neutrophil Count	• Insulin
AST (SGOT)				• Glucose
ALT (SGPT)				• c-peptide
				• Free fatty acids
				• Glucagon
				Serum PD
				Serum endogenous GDF15
				Lipid Panel[b]
				• HDL
				• LDL
				• Triglycerides
				• Cholesterol
				HbA1c[b]

Footnotes defined on next page of the table.
[a] HIV assessment is recommended
[b] Lipid panel and HbA1c are to be run by local lab at screening and central lab at all other time points
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; **FSH = follicle stimulating hormone; HbA1C = hemoglobin A1C;** HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; **PD = pharmacodynamic; PK = pharmacokinetic;** PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

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 non-voting Amgen representatives may also be part of the DLRT: clinical study manager, biostatistician, or **pharmacokinetic (**PK**)** 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, IP administration, medical history, concomitant medications, adverse events, ECG, vital signs, and laboratory results will be reviewed. Data to be reviewed may 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.

DLRM 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 the Site Investigators or delegates combined. Regardless of how many Site Investigators there are, all 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%).

DLRM 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 Conference on 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 **that Amgen distributes to the site**. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

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 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 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 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 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.

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 (ICF) 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

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 IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

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 pre-study 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

Non-investigational 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 SAP.

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.

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 **Assessment of seriousness;** o Severity (or toxicity defined below); o Assessment of relatedness to investigational product**;** 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 (CRO) 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 shown below:**	
Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product or study-mandated procedure and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred, and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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. 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 **the paper-based Serious Event Contingency Report Form**.

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

AMGEN Study # 20180244 AMG 171	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

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome 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 171 No✓ Yes✓ / <Device> No✓ Yes✓ / <Device> No✓ Yes✓ / <Device> 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 171	☒ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test / Unit											
	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20180244 AMG 171	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 Sections 5.1 and 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 2 and half 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 post-menopausal 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 2 and half months after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal, IUD, IUS, 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

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

- Periodic abstinence (calendar, symptothermal, post-ovulation 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 2 and half months after last dosed of AMG 171/placebo.
- 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 2 and half months of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or 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 post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in 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 2 and half 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 2 and half month of receiving last dose of study drug.
- 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 238.

- 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 2 and half 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: 20180244

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
•AMG 171				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: 20180244

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 171				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 (biomarker, pharmacokinetics (PK) 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 obesity and other metabolic conditions, the dose response and/or prediction of response to AMG 171 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, biomarker development 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*.

11.7.1 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 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, rhabdomy**oly**sis, hemolysis)

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

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

Table 11-2. 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

11.7.2 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 study drug is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-2) are never to be rechallenged.

11.7.3 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 11-2 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, bilirubin (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 non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for 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 Columbia-Suicide Severity Rating Scale (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 sores have been identified.

Table 11-3. 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 11-3 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 3

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 171 in Subjects With Obesity

Amgen Protocol Number AMG 171 20180224

Amendment Date: 18 August 2021

Rationale:

Additional dose cohorts are being added to explore higher exposures and dose titration regimens that will limit tolerability issues of nausea and vomiting.

This protocol is being amended to:

- Update the study design: AMG 171 or placebo will be administered subcutaneously (SC). Part D is comprised of approximately 48 subjects enrolling into 1 of 6 cohorts. Enrollment into cohorts 6a and 7a will begin contemporaneously after a Dose Level Review Meeting (DLRM) of cohorts 4 and 5, respectively. Enrollment in cohorts 6b and 7b will occur after Dose Level Review Team (DLRT) recommendation based on safety and laboratory data through at least study day 43 of cohort 6a (Part D). Subsequently, cohorts 6c and 7c will be dosed in parallel after the dose regimen in cohort 6b has been recommended by the DLRT to be safe and reasonably tolerated based on safety and laboratory data through at least study day 57 for at least 6 out of 8 subjects dosed.
- Update the AMG 171 dosing (Part D):
    - Cohort 6a: Study drug will be administered SC every 2 weeks (Q2W) for a total of 7 doses [redacted]
    - Cohort 6b: Study drug will be administered SC Q2W for a total of 7 doses [redacted]
    - Cohort 6c: Study drug will be administered SC Q2W for a total of 7 doses [redacted]

- Cohort 7a: Study drug will be administered SC weekly (Q1W) for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].
- Cohort 7b: Study drug will be administered SC Q1W for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].
- Cohort 7c: Study drug will be administered SC Q1W for a total of 4 doses [redacted] and then Q2W for a total of 4 additional doses [redacted].

- Update the number of subjects planned to be enrolled for Part D
- Administrative, typographical, and formatting changes were made throughout all documents.

Amendment 2

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 171 in Subjects With Obesity

Amgen Protocol Number AMG 171 20180224

Amendment Date: 28 October 2020

Rationale:

This protocol amendment addresses changes to study design after nausea and vomiting treatment-emergent adverse events (TEAEs) of moderate severity were reported in cohort 1b [redacted] mg subcutaneous [SC]) and met protocol-specified stopping rule criteria. Adverse reactions of transient nausea and vomiting have been observed with other glucagon-like peptide 1R (GLP-1R) agonists drugs approved for chronic weight management in obese and overweight adults (eg, liraglutide) and have been associated with greater weight loss, suggesting an on-target pharmacodynamic effect. In general, these reported side effects of other GLP-1 agonists were tolerable with the percentage of patients reporting nausea declining as treatment continued. The observed TEAEs for AMG 171 may also reflect on-target pharmacodynamic activity. This amendment incorporates adjustments to the dosing plan, to assess if dose titration and low fixed dose multiple dosing for AMG 171 help mitigate the side effects of nausea and vomiting.

This protocol is being amended to:

- Update the study design: AMG 171 will be administered SC. Part A is comprised of 2 single ascending dose cohorts, Part B is a multiple dose cohort, and Part C is a titration phase with step dosing ranging from 2 to 3 ascending doses. The study consists of a total of 6 cohorts: 2 cohorts (Part A), 1 cohort (Part B), and 3 cohorts (Part C).
- Update the AMG 171 dosing:

- Part A: As tolerability was noted to worsen with the dose increase from [redacted] mg (cohort 1) to [redacted] mg (cohort 1b) with adverse events of nausea and vomiting (mild to moderate severity), multiple doses of the lower more tolerated dose [redacted] mg will be evaluated in Part B, and titration and Part A dose levels will be evaluated in Part C.
- Part B: Approximately 8 subjects will enroll into 1 cohort 8 subjects will be randomized to receive AMG 171 or placebo SC in a 3:1 ratio. Enrollment of subsequent cohorts (Part C) will occur once recommended by the Dose Level Review Team (DLRT) after safety and laboratory data through at least study day 22 for at least 6 out of 8 subjects dosed in cohort 2 (Part B) is deemed to be safe and reasonably tolerated.
- Part C: Approximately 24 subjects will enroll into 1 of 3 cohorts. In each cohort, 8 subjects will be randomized to receive AMG 171 or placebo SC in a 3:1 ratio. Enrollment into cohort 3 will occur after DLRT recommendation based on safety and laboratory day through at least study day 22 of cohort 2 (Part B). Subsequently, cohorts 4 and 5 will be dosed after the dose regimen in the cohort 3 has been recommended by the DLRT to be safe and reasonably tolerated based on safety and laboratory data through day 22 for at least 6 out of 8 subjects dosed.

- Update the number of subjects planned to be enrolled (approximately 48 subjects [8 subjects per cohort, cohorts 1, 1b, 2-5]).
- Additional study days were added to each cohort.
- Update the planned study duration:
  - Part A is approximately 120 days, Part B is 207 days, and Part C cohort 3 is 85 days, cohort 4 is 113 days, and cohort 5 is 85 days.
- Update that the primary analysis will occur with the final analysis.
- Administrative, typographical, and formatting changes were made throughout all documents.

Amendment #1

Protocol Title: **A Phase 1, Randomized, Double-blind, Placebo-controlled, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 171 in Subjects With Obesity**

Amgen Protocol Number: AMG 171 20180224

Amendment Date: 07 February 2020

Rationale:

Protocol was amended to include an additional intermediate cohort (lower dose than planned) between cohort 1 and 2, and to revise dosing for future cohorts pending safety review of completed cohorts. Main changes to the protocol include:

- Addition of cohort 1b dosing at [redacted] mg (due to mild adverse events of nausea observed in cohort 1 suggesting a pharmacodynamic effect at initial low dose)
- Addition of ADA sample collection at Day 15
- Addition of ECG 10min post dose in cohort 6 IV dosing
- Removing Gastric emptying test in cohort 6 IV dosing
- Collection of photographs during local injection site reactions, if appropriate
- Collection of additional ADA samples within 30 min if subject experiences a hypersensitivity reaction