Statistical Analysis Plan

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
NCT Number:	04199351
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	9 April 2020	NA
[Amendment 1 (v2.0)]	1st February 2022	1.0 Introduction **Replace:** The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 1 for study 20180224, AMG 171 dated 07 February 2020. **With:** The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol **amendment 2** for study dated 20180224, AMG 171 **28 October 2020**. 2.1 Objective and Endpoints **Replace:** • To assess the effect of AMG 171 on hemoglobin A1c (HbA1c) in the multiple dose cohorts (Parts B and C) • To assess the effect of AMG 171 on body composition in the multiple dose cohorts (Parts B and C) **With:** • To assess the effect of AMG 171 on hemoglobin A1c (HbA1c) in the multiple dose cohorts (**Parts B**) • To assess the effect of AMG 171 on body composition in the multiple dose cohorts (**Parts B**)

		3.1 Study Design **Replace:** 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) or intravenously (IV) (Part A: cohort 6 only). Part A will be a single ascending dose (SAD) phase; Part B will be a multiple ascending dose phase; and Part C will be an expansion cohort. The study consists of a total of 12 cohorts: 7 cohorts (Part A), 4 cohorts (Part B), and 1 cohort (Part C). 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 Day -2) through the morning of Day 6 in Part A (SAD phase), from Day -1 to Day 1 in Part B, or optionally from Day -1 to Day 1 (Part C). **Part A** Approximately 56 subjects will enroll into one of 7 cohorts. In each cohort, eight (8) subjects will be randomized to receive AMG 171 or placebo SC (cohorts 1, 1b, 2-5) or IV (cohort 6) in a 3:1 ratio as described in Table 3-1. For each cohort,

		the first 2 subjects (sentinel pair) will be randomized such that 1 subject will receive AMG 171 and 1 subject will receive placebo. The sentinel pair will be observed for at least 24 hours before the remaining subjects in the cohort are dosed, provided there are no safety or tolerability concerns as assessed by the Principal Investigator (PI). Enrollment into the SAD cohorts will be sequential. Subsequent cohorts will be dosed after the dose regimen in the preceding cohort has been recommended by the Dose Level Review Team (DLRT) to be safe and reasonably tolerated based on the safety and laboratory data through at least study day 15 for at least 7 out of 8 subjects dosed. **Part B** Approximately 32 subjects will enroll into one of 4 cohorts. In each cohort, eight (8) subjects will be randomized to receive AMG 171 or placebo SC in a 3:1 ratio as described in Table 3-1. Enrollment into Part B will occur with a starting dose that is at least 2 SAD dose levels below what was recommended by the DLRT to be safe and reasonably tolerated in Part A. DLRT recommendations will be based on safety and laboratory data through at least study day 15 for at least 7 out of 8 subjects dosed in each SAD cohort (Part A). Enrollment into the remaining cohorts

		will be sequential. Subsequent cohorts will be dosed after the dose regimen in the preceding cohort has been recommended by the DLRT to be safe and reasonably tolerated based on safety and laboratory data through at least study day 36 for a minimum of 6 out of the 8 subjects dosed. All subjects in each Part B cohort may be dosed on the same day. • **Cohorts 7-9**: Study drug will be administered every 4 weeks (Q4W) for a total of 3 SC doses. The dose levels will be defined after evaluation of the available PK and PD data from preceding cohorts in Part A (SAD). Three different dose levels will be evaluated with the lowest dose administered to cohort 7, and two higher ascending doses administered to cohorts 8 and 9. The dose level for cohorts 7-9 will not exceed the highest dose evaluated in cohorts 1-6 (Part A), including cohort 1b. • **Cohort 10:** Study drug will be administered every 2 weeks (Q2W) for a total of 6 SC doses. The dose level will be defined after evaluation of the available PK and PD data from proceeding cohorts. The dose level will not

		exceed half the highest dose evaluated in cohorts 7-9 (Part B). **Part C** Up to 60 subjects will enroll into cohort 11. All subjects will be randomized in a 1:1 ratio to receive AMG 171 or placebo SC as described in Table 3-1. Enrollment into cohort 11 (Part C) will occur after the dose regimen in previous cohorts (Part B) has been recommended by the DLRT to be safe and reasonably tolerated based on safety and laboratory data through at least study day 36 for a minimum of 6 of the 8 subjects dosed. The dose regimen for cohort 11 will be chosen based on the preceding cohorts' available safety and PK data and will not exceed the highest dose evaluated in cohorts 7-9. **Dose Level Review Meetings (DLRM)** DLRM will be held to review subject data and monitor safety before escalation to the next cohort. Escalation to a higher dose cohort will only proceed when the previous dose regimen has been found to be safe and reasonably tolerated based on available safety and laboratory data through day 15 for at least 7 out of 8 subjects dosed in each cohort in Part A, and day 36 for a minimum of 6 of the 8 subjects dosed in each cohort in Part B, and upon unanimous recommendation at the DLRM.

Table 3-1. 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	Not exceeding [redacted] mg Day 1 x 1	SC	6:2
	1b[d]	8	Not exceeding [redacted] mg Day 1 x 1	SC	6:2
	2	8	Not exceeding [redacted] mg Day 1 x 1	SC	6:2
	3	8	Not exceeding [redacted] mg Day 1 x 1	SC	6:2
	4	8	Not exceeding [redacted] mg Day 1 x 1	SC	6:2
	5	8	Not exceeding [redacted] mg Day 1 x 1	SC	6:2
	6	8	Not exceeding [redacted] mg Day 1 x 1	IV	6:2
PART B	7	8	Dose 1 TBD[a] Q4W x 3	SC	6:2
	8	8	Dose 2 TBD[a] Q4W x 3	SC	6:2
	9	8	Dose 3 TBD[a] Q4W x 3	SC	6:2
	10	8	Dose 4 TBD[b] Q2W x 6	SC	6:2
PART C	11	60	Dose TBD[c] Q4W x 3 based on the available safety, PK and PD from cohorts 7-10 (Part B)	SC	30:30

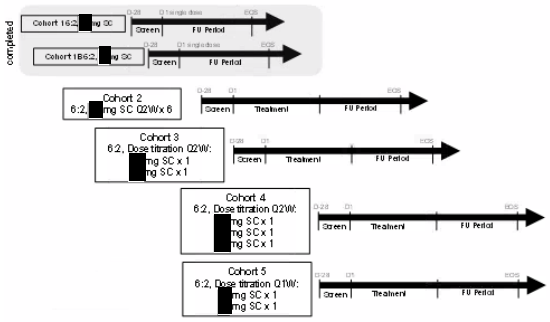
[a] Dose will not exceed highest dose evaluated in cohorts 1-5 (Part A), including cohort 1b
[b] Dose will not exceed half the highest dose evaluated in cohorts 7-9 (Part B)
[c] Dose will not exceed highest dose evaluated in cohorts 7-9 (Part B)
[d] Cohort 1b added during protocol amendment 1

With:

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.** The study consists of a total of **6** cohorts: **2** cohorts (Part A; SAD), **1** cohort (Part B), and **3** cohorts (Part C; **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 Day −**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 -14 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. **Part B** **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 3.1.** **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 3.1**. 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). Subsequent**ly, both** cohort **4 and 5** will be dosed after the dose regimen in cohort **3** has been recommended by the DLRT to be safe and reasonably tolerated based on safety and laboratory data through at least study day **22** for **at least** 6 out of 8 subjects dosed. Enrollment of dose cohorts is depicted in Figure 3.1. Figure 3.1. Planned Dose Levels by Cohort in Parts A, B and C  **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 be safe and reasonably tolerated based on available safety and laboratory data upon unanimous recommendation at the DLRM. **Safety and laboratory data was reviewed through day 15 for at least 7 out of 8 subjects dosed in Part A and**

through day 22 for at least 6 of 8 subjects dosed in Part B and Part C.

Table 3.1. 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	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

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

3.2 Sample Size

Replace:

Approximately 148 subjects (8 subjects per cohort, cohorts 1, 1b, 2-10; up to 60 subjects in cohort 11) will be enrolled. Additional subjects may be enrolled if a DLRT recommendation is made to expand, repeat or add cohorts to the study. The sample size for the study is based on practical considerations. No statistical hypothesis will be tested. For safety considerations, with up to 96 subjects (66 subjects from Part A and B, 30 subjects from Part C) receiving AMG 171, the chance of detecting an adverse event with a true incidence rate of 2% or greater is more than 85% and the chance of detecting an adverse event with a true incidence rate of 4% or greater is more than 98%.

Cohort 11 (Part C) with 1:1 randomization will allow for 80% probability of observing a mean treatment difference in percent

		change from baseline in body weight between AMG 171 and placebo of > 3%, assuming a true treatment difference of 5% at week 12 which represents clinically meaningful weight loss. This assumes a standard deviation for percent change from baseline in body weight of 7% in each treatment group. **With:** Approximately **48** subjects (8 subjects per cohort, cohorts 1, 1b, 2 **to 5**) will be enrolled. Additional subjects may be enrolled if a DLRT recommendation is made to expand, repeat or add cohorts to the study. The sample size for the study is based on practical considerations. No statistical hypothesis will be tested. For safety considerations, with up to **36** subjects (**12** subjects from Part A, **6 subjects in Part B,** and **18** subjects from Part C) receiving AMG 171, the chance of detecting an adverse event with a true incidence rate of **3**% or greater is larger than **67**% and the chance of detecting an adverse event with a true incidence rate of **5**% or greater is larger than **84**%. 5.0 Defintions **Replace:** **Treatment-Emergent Adverse Event:** A treatment-emergent adverse event (TEAE) is any adverse event that is categorized as an Adverse Event (AE)

		starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Events eCRF and up to the End of Study date. **With:** **<u>Treatment-Emergent Adverse Event:</u>** Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF and up to the End of Study date. **Definition Added:** **<u>Treatment-Emergent Serious Adverse Event:</u>** Treatment-emergent adverse events indicated as serious on the Events eCRF. **Replace:** **<u>Baseline ECG:</u>** For cohort 1 to 10 subjects, baseline ECG will be calculated as the average of the available pre-dose observations (9 observations) taken on Day 1. If any of the observations are missing, the mean will be calculated by taking the available observations. If all Day 1 pre-dose observations are missing, the baseline will be calculated in the same way using

		the last assessment before first dose of IP. For cohort 11 subjects, baseline ECG is defined as the single pre-dose observation taken on Day 1. If the Day 1 pre-dose observation is missing, the last assessment taken before investigational product will be used. **With:** **<u>Baseline and Post-baseline ECG:</u>** Where multiple 12-lead ECG measurements are taken at the same assessment time point (they are planned to be recorded in triplicate 30 seconds apart) the mean value will be calculated and used in the analysis. The baseline ECG is defined as the mean of all the pre-dose assessments measured on Study Day 1; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages. For pre and post dose ECG measurements, unscheduled ECG measurements taken up to 5 minutes after the last assessment of a triplicate will be included in the averages for a time point. Where an ECG is missing within a triplicate, all available data will be averaged for that time point. **Replace:** **<u>End of Study:</u>** 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. **With:** **<u>Subject-level End of Study (EOS) Date:</u>** End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page. **Definition Added:** **<u>Baseline and Post-baseline BMI:</u>** Baseline and Post-baseline BMI is to derive by Baseline height and respective visit of the weight measurement. BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2. **<u>End of IP (EOIP) Date:</u>** **End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of IP CRF page.** **<u>Last IP Dose Date:</u>** **Last IP Dose Date for each subject is defined as the latest date IP is administered.** **<u>Duration of IP Exposure in Weeks</u>** Duration of IP exposure (weeks) = (Last Dose IP Date – Study Day 1+ 1) / 7

		Duration of Study Exposure in Weeks Duration of Study exposure (weeks) = (EOS Date - Study Day 1 + 1) / 7 **Definition Removed:** **Bazett-corrected QT Interval (QTcB)** The Bazett's correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcB=QT/(RR/1000)^{1/2}$ 6.0 Analysis Sets **Replace:** The following analysis sets may be separately defined for SAD (cohort 1-6), cohort 7-10 and extension cohort 11. **With:** The following analysis sets may be separately defined for part A (SAD cohort 1 and 1b), part B (cohort 2) and part C (titration cohort 3-5). **Definition Added:** 6.1 Full Analysis Set (FAS) **The full analysis set will consist of all subjects who receive at least one dose of investigational product.** 6.2 Safety Analysis Set (SAS) **Replace**: The safety analysis set will consist of all subjects who receive at least one dose of investigational product. **With**:

		The safety analysis set is defined as same to the FAS. 6.3 Pharmacodynamic (PD) Analysis Set **Removed** 7.2 Priimary Analysis **Replace:** The primary analysis will occur after all subjects in cohort 1 to 10 (including cohort 1b) have completed the study. Data will be locked prior to conducting the primary analysis based on a clean snapshot of data from cohort 1 to 10. **With:** 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 data will be used for the primary analysis.** 7.3 Final Analysis **Replace:** The final analysis will occur after all subjects in cohort 11 have completed the study. Data will be locked prior to conducting the final analysis based on a clean snapshot of data from cohort 11. **With:** The **primary analysis will be the** final analysis **for this** study. 9.0 General Considerations **Replace:**

		Data for subjects receiving placebo may be combined across cohorts within Part A and Part B, separately. **With:** Data for subjects receiving placebo may be combined across cohorts within Parts A, **B**, and **C**. 9.4 Demographic and Baseline Characteristics **Replace:** Demographic (ie. age, age groups [< 40, >= 40], sex, race, ethnicity) and baseline characteristics (height, weight, body mass index, medical history) will be summarized by cohort and actual treatment group and overall (i.e. total from all the cohorts involved in the analysis and irrespective of treatment received) using descriptive statistics. **With:** Demographic (ie. age, age groups [< 40, >= 40, **<18, 18-64, ≥65**],], sex, race, ethnicity) and baseline characteristics (height, weight, body mass index, medical history) will be summarized by cohort and actual treatment group and overall (i.e. total from all the cohorts involved in the analysis and irrespective of treatment received) using descriptive statistics. 9.6.1 Analysis of Primary Safety Endpoint(s) **Replace:**

Table 9-1. Safety Endpoint Summary Table

Endpoint	Statistical Analysis Methods	Sensitivity Analysis
Subject incidence of treatment-emergent adverse events (TEAEs)	Following analysis will be performed for safety analysis set by part (Part A, B and C) and actual treatment group. • Subject incidence of ▪ TEAEs by system organ class (SOC) and preferred term (PT) ▪ Serious adverse events (SAEs)by SOC/PT ▪ Fatal events by SOC/PT ▪ TEAEs leading to withdrawal from IP or other protocol-required therapies by SOC/PT ▪ TEAEs by SOC, PT and grade ▪ SAEs by SOC, PT and grade ▪ Treatment related TEAEs by SOC/PT	Not Applicable
▪ Changes in laboratory safety tests, vital sings and 12-lead ECGs	Following analysis will be performed for SAS by part (Part A, B and C) and actual treatment group at protocol-specified scheduled visit. • Summary statistics of ▪ Change from baseline safety laboratory test results ▪ Change from baseline vital signs ▪ Changes from baseline ECG parameters	Not Applicable

With:

Table 9.1. Safety Endpoint Summary Table

Endpoint	Statistical Analysis Methods	Sensitivity Analysis
Subject incidence of treatment-emergent adverse events (TEAEs)	Following analysis will be performed for safety analysis set by part (Part A, B and C) and actual treatment group. • Subject incidence of ▪ Fatal events by SOC/PT ▪ TEAEs leading to withdrawal from IP or other protocol-required therapies by SOC/PT ▪ TEAEs by SOC, PT and grade ▪ SAEs by SOC, PT and grade	Not Applicable
▪ Changes in laboratory safety tests, vital sings and 12-lead ECGs	Following analysis will be performed for SAS by part (Part A, B and C) and actual treatment group at protocol-specified scheduled visit. • Summary statistics of ▪ Change from baseline safety laboratory test results ▪ Change from baseline vital signs ▪ Changes from baseline ECG parameters	Not Applicable

9.6.2 Adverse Events

Replace:

The subject incidence of adverse events will be summarized for all TEAEs, SAEs, TEAEs leading to withdraw of IP, fatal adverse events, treatment related TEAEs and adverse events of interest (EOIs).

Subject incidence of all TEAEs, SAEs, TEAEs leading to withdrawal of IP, fatal adverse events, and treatment related TEAEs will be tabulated by SOC and PT in descending order of frequency.

Immunogenicity, Injection site reactions and Nausea/vomiting will be identified using Amgen-defined MedDRA search strategies.

With:

The subject incidence of adverse events will be summarized for all TEAEs, SAEs, TEAEs leading to withdraw of IP, fatal adverse events, and adverse events of interest (EOIs).
Subject incidence of all TEAEs leading to withdrawal of IP, fatal adverse events, and will be tabulated by SOC and PT in descending order of frequency.
Immunogenicity, Injection site reactions and Nausea/vomiting will be identified using **a broad search/scope in** Amgen-defined MedDRA search strategies.

9.6.3 Laboratory Test Results

Replace:

For key laboratory parameters which are given in Table A below, summary statistics will be provided for actual value, change from baseline and percent change from baseline by study part (Part A, B and C), actual treatment group at each protocol-specified scheduled visit.

Local Laboratory (Chemistry): Sodium, Potassium, Chloride, Bicarbonate, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Glucose, BUN or Urea, Creatinine, Uric acid, Total bilirubin, Direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT)
Local Laboratory (Coagulation): PT/INR, APTT
Local Laboratory (Urinalysis): Specific gravity, pH
Local Laboratory (Hematology): RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, Reticulocytes, Platelets, WBC Differential • Eosinophils • Basophils • Lymphocytes • Monocytes • Total Neutrophil Count
Other Local Laboratory: TSH, Lipid Panel[a] • HDL • LDL • Triglycerides • Cholesterol, HbA1c[a]
Central Laboratory: Antibodies, Serum PK, Plasma PD: • Insulin • Glucose • c-peptide •Free fatty acids • Glucagon, Serum PD, Serum endogenous: GDF15, Lipid Panel[a] • HDL • LDL • Triglycerides •Cholesterol, HbA1c[a]

With:

For key laboratory parameters which are given in Table 9.2 below, summary statistics will be provided for actual value, change from baseline and percent change from baseline by study part (Part

		A, B and C), actual treatment group at each protocol-specified scheduled visit. **Table 9.2. Laboratory parameters** Local Laboratory (Chemistry): Sodium, Potassium, Chloride, Bicarbonate, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Glucose, BUN or Urea, Creatinine, Uric acid, Creatine kinase, Total bilirubin, Direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT) Local Laboratory (Urinalysis): Specific gravity, pH Local Laboratory (Hematology): RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, Reticulocytes, Platelets, WBC, Differential • Eosinophils • Basophils • Lymphocytes • Monocytes • Total Neutrophil Count Central Laboratory: Antibodies, Serum PK, Plasma PD: • Insulin • Glucose • c-peptide • Glucagon, Serum PD: •Free fatty acids, Lipid Panel[a] • HDL • LDL • Triglycerides •Cholesterol, HbA1c[a] 9.6.6 Electrocardiogram **Replace:** Summary statistics for all ECG parameters (QRS, QT, QTc, RR, PR, QTcF and QTcB) will be provided for actual value, change from baseline and percent change from baseline by study parts (Part A, B and C) and actual treatment group at each specified protocol scheduled visit. Further, subjects' maximum change from baseline in QTcF and QTcB will be categorized in following categories and the number and percentage of subjects in each group will summarized by study parts (Part A, B and C) and actual treatment group. Unscheduled assessments will be included in the determination of the maximum change. • ≤ 30 msec • > 30 – 60 msec • > 60 msec Subjects' maximum post baseline values in QTcF and QTcB will also be categorized in the following categories and the number and percentage of subjects in each group will be summarized.

		• ≤ 450 msec • > 450 – 480 msec • > 480 – 500 msec • > 500 msec Listings of all on-study ECG measurements may be generated and reviewed but may not be included in the CSR. **With:** Summaries over time and changes from baseline over time will be provided for all 12-lead ECG parameters (QRS, QT, RR, PR, and QTcF) by study parts (Part A, B and C) and actual treatment group at each specified protocol scheduled visit. The analysis Fridericia's (QTcF) QT correction will be performed using the derived results as specified in Section 5. Subjects will be categorized into the following groups per their maximum change from baseline in QTcF. Unscheduled assessments will be included in the determination of the maximum change. • ≤ 30 msec • > 30 – 60 msec • > 60 msec Subjects will also be categorized into the following groups per their maximum post baseline QTcF. Unscheduled assessments will be included in the determination of the maximum post baseline value. • ≤ 450 msec

		• > 450 – 480 msec • > 480 – 500 msec • > 500 msec All on-study electrocardiogram (ECG) data will be listed and reviewed but may not be included in the CSR. 9.7.1 Secondary Endpoint - Pharmacokinetics Analysis **Removed:** 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_{0-5h} as well as maximum plasma acetaminophen concentrations (C_{max}), and time of C_{max} (T_{max}). 9.7.2.1 Pharmacodynamic Parameters **Replace:** • HbA1c levels (Part B and C only). • Body composition parameters (eg. Fat, muscle and bone mineral content) measured by Dual-energy x-ray absorptiometry (Part B and C only). **With:** • HbA1c levels (**Part B only**). • Body composition parameters (eg. Fat, muscle and bone mineral content) measured by Dual-

		energy x-ray absorptiometry (**Part B only**). 9.7.2.1 Pharmacodynamic Parameters **Removed** • Gastric emptying as assessed by acetaminophen absorption kinetics (C_{max} and AUC) (Part A only). • Potential biomarkers including, but not limited to, inflammatory and adipose tissue markers • Endogenous GDF15 levels 10. Changes From Protocol-specified Analyses **Replace:** There are no changes to the protocol-specified analyses **With:** **No PK and pharmacodynamic (PD) analysis will be performed for gastric emptying test. PD analysis set will also not be created.**

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	adverse event(s)
AUC	area under the concentration-time curve
BMI	body mass index
C_{max}	maximum serum concentration
DLRM	Dose level review meeting
DLRT	Dose level review team
DXA	Dual-energy x ray absorptiometry
ECG	12-lead electrocardiogram
eCRF	electronic case report form
FFA	Free Fatty Acid
IP	Investigational product
IPD	Important protocol deviation
LDL-C	Low-density lipoprotein cholesterol
LLQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic(s)
PI	Principle investigator
PK	Pharmacokinetic(s)
PT	Preferred term
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG

QTc interval	QT interval corrected for heart rate using accepted methodology
QTcF	Fridericia-corrected QT Interval
Q2W	every 2 weeks
Q4W	every 4 weeks
RR	respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SC	Subcutaneous
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment emergent adverse event
T_{max}	time to maximum serum concentration
EOS	End of Study
Safety FU	Safety Follow-Up

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the **protocol amendment 2** for study 20180224, AMG 171 dated **28 October 2020**. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 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 o To assess the effect of AMG 171 on fasting and post-prandial (Part A) metabolic parameters o To assess the effect of AMG 171 on gastric emptying in the single ascending dose cohorts (Part A) o To assess the effect of AMG 171 on fasting lipid levels o To assess the effect of AMG 171 on hemoglobin A1c (HbA1c) in the multiple dose cohorts (**Part B**) o To assess the effect of AMG 171 on potential biomarkers o To assess the effect of AMG 171 on endogenous GDF15 levels o To assess the effects of AMG 171 on body weight, waist circumference and body mass index (BMI) o To assess the effect of AMG 171 on body composition in the multiple dose cohorts (**Part B**)	• Changes in pharmacodynamic parameters: o Changes in the fasting and post-mixed meal challenge glucose, insulin, c-peptide, glucagon, and free fatty acid (FFA) concentrations o Gastric emptying as assessed by acetaminophen absorption kinetics (C_{max} and AUC) o 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 o Changes in HbA1c levels o Changes in potential biomarkers including, but not limited to, inflammatory and adipose tissue markers o Changes in endogenous GDF15 levels o Changes in body weight, waist circumference, and BMI o Changes in body composition as measured by whole body dual-energy x-ray absorptiometry (DXA)

2.2 Hypotheses and/or Estimations

No statistical hypotheses will be tested in this study.

3. Study Overview

3.1 Study 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.** The study consists of a total of **6** cohorts: **2** cohorts (Part A; SAD), **1** cohort (Part B), and **3** cohorts (Part C; **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 Day −**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 -14 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.**

Part B

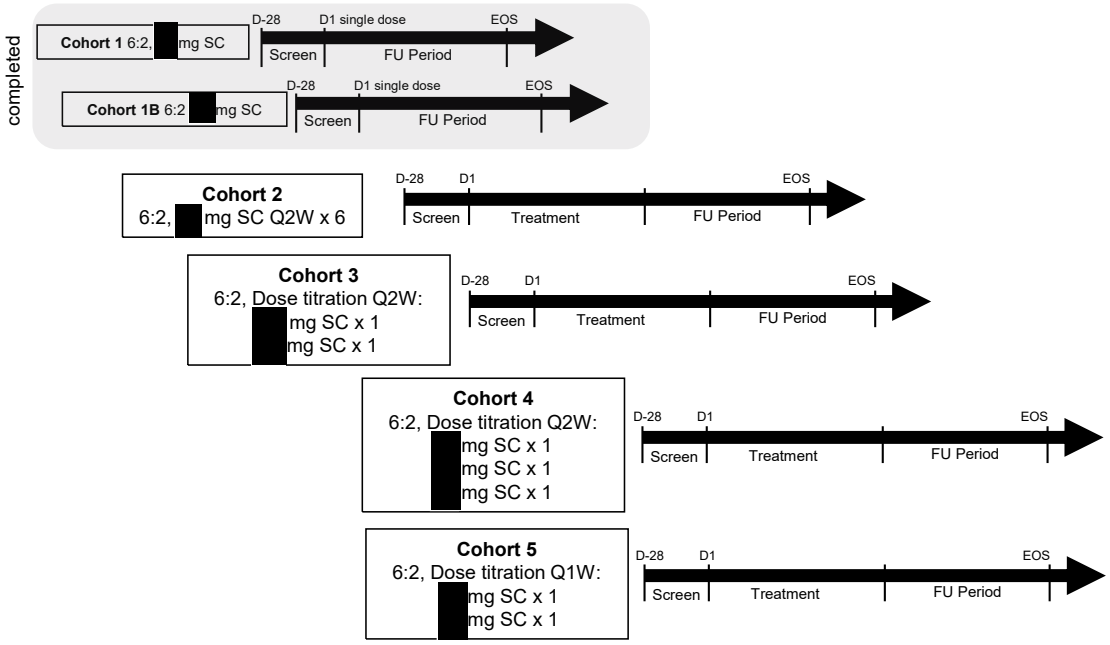
Approximately 8 subjects will enroll into 1 cohort (cohort 2) where 8 subjects will be randomized to receive AMG 171 or placebo SC in a 3:1 ratio as described in Table 3.1.

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 3.1**. 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). Subsequent**ly, both** cohort **4 and 5** will be dosed after the dose regimen in cohort **3** has been recommended by the DLRT to be safe and reasonably tolerated based on safety and laboratory data through at least study day **22** for **at least** 6 out of 8 subjects dosed. Enrollment of dose cohorts is depicted in Figure 3.1.

Figure 3.1. Planned Dose Levels by Cohort in Parts A, B and C



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 be safe and reasonably tolerated based on available safety and laboratory data upon unanimous recommendation at the DLRM.

Safety and laboratory data was reviewed through day 15 for at least 7 out of 8 subjects dosed in Part A and through day 22 for at least 6 of 8 subjects dosed in Part B and Part C.

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.

Table 3.1. 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	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

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

3.2 Sample Size

Approximately **48** subjects (8 subjects per cohort, cohorts 1, 1b, 2 **to 5**) will be enrolled. Additional subjects may be enrolled if a DLRT recommendation is made to expand, repeat or add cohorts to the study. The sample size for the study is based on practical considerations. No statistical hypothesis will be tested. For safety considerations, with up to **36** subjects (**12** subjects from Part A, **6 subjects in Part B,** and **18** subjects from Part C) receiving AMG 171, the chance of detecting an adverse event with a true incidence rate of **3**% or greater is larger than **67**% and the chance of detecting an adverse event with a true incidence rate of **5**% or greater is larger than **84**%.

3.3 Adaptive Design

Not applicable.

4. Covariates and Subgroups

4.1 Planned Covariates

Baseline values may be used as a covariate in analyses.

4.2 Subgroups

No subgroup analyses are planned.

5. Definitions

Actual Treatment Group:

A subject's actual treatment group is defined as the treatment received, where subjects who received ≥ 1 dose of AMG 171 will be analyzed in the AMG 171 treatment group regardless of the randomized treatment.

Age:

Subject age at randomization will be determined using the age in years reported in the clinical database.

Treatment-Emergent Adverse Event:

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by "Did event start before first dose of investigational product" equal to "No" or missing on the Events eCRF and up to the End of Study date.

Treatment-Emergent Serious Adverse Event:

Treatment-emergent adverse events indicated as serious on the Events eCRF.

Baseline:

For any variable, unless otherwise defined, baseline is the last non-missing assessment taken prior to the first dose of investigational product.

Baseline and Post-baseline BMI:

Baseline and Post-baseline BMI is to derive by Baseline height and respective visit of the weight measurement.

BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2.

Baseline and Post-baseline ECG:

Where multiple 12-lead ECG measurements are taken at the same assessment time point (they are planned to be recorded in triplicate 30 seconds apart) the mean value will be calculated and used in the analysis. The baseline ECG is defined as the mean of all the pre-dose assessments measured on Study Day 1; the mean of values in a triplicate should be calculated before taking the mean of the triplicate averages. For pre and post dose ECG measurements, unscheduled ECG measurements taken up to 5 minutes after the last assessment of a triplicate will be included in the averages for a time point. Where an ECG is missing within a triplicate, all available data will be averaged for that time point.

Change from Baseline:

The change from baseline is defined as the arithmetic difference between a post-baseline value and baseline for a given time point:

Change from Baseline = (post-baseline value – baseline value)

Percent Change from Baseline:

The percent change from baseline for a given variable at a given time point is defined as:

Percent Change from Baseline =

[(post-baseline Value – baseline Value) / baseline Value] x 100

Investigational Product (IP):

The investigational products are defined as AMG 171 and placebo.

Subject-level End of Study (EOS) Date:

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

End of IP (EOIP) Date:

End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of IP CRF page.

Last IP Dose Date:

Last IP Dose Date for each subject is defined as the latest date IP is administered.

Study Day 1:

Day 1 is defined as the date that the first dose of investigational product is administered.

Study Day:

For study date later than Study Day 1:

Study Day = (study date - date of Study Day 1) + 1

For study date earlier than Study Day 1:

Study Day = (study date – date of Study Day 1)

Duration of IP Exposure in Weeks

Duration of IP exposure (weeks) = (Last Dose IP Date – Study Day 1+ 1) / 7

Duration of Study Exposure in Weeks

Duration of Study exposure (weeks) = (EOS Date - Study Day 1 + 1) / 7

Fridericia-corrected QT Interval (QTcF)

The Fridericia correction will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: QTcF=QT/ (RR/1000) ^0.33.

6. Analysis Sets

The following analysis sets may be separately defined for part A (SAD cohort 1 and 1b), part B (cohort 2) and part C (titration cohort 3-5).

6.1 Full Analysis Set (FAS)

The full analysis set will consist of all subjects who receive at least one dose of investigational product.

6.2 Safety Analysis Set (SAS)

The safety analysis set is defined as same to the FAS.

6.3 Pharmacokinetic (PK) Analysis Set

The PK analysis set will consist of all subjects who receive at least one dose of AMG 171 for whom at least one concentration post-dose or PK parameter or endpoint can be adequately estimated. The subjects in cohort 4 who received expired IP are not included in the PK analysis set.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

Members of DLRT 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 of 11.3 of the protocol for further details.

7.2 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 data will be used for the primary analysis.

7.3 Final Analysis

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

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

In the event that data is not available for a subject, no imputations will be done for the missing data.

Laboratory measurements that are below the quantification limits will be considered equal to the lower limit of quantification (LLQ) for the calculation of population averages in summary tables. There will be no imputation of clinical laboratory values below LLQ for individual subject level data in line listings, as applicable.

Biomarker data that are below the quantification limits will be considered equal to half of the LLQ for all analyses unless specified otherwise.

PK concentrations that are below the quantification limits will be set to zero when engaging non-compartmental model to compute PK parameters.

For partial dates (such as for adverse event and concomitant medication, etc.), imputation of dates will be carried out as per Appendix A.

8.4 Detection of Bias

Protocol compliance will be examined by listing important protocol deviations (IPD) by cohort and site.

8.5 Outliers

Outliers may be identified via the use of descriptive statistics. All data confirmed as an outlier will not be excluded in the analyses described in this statistical analysis plan.

If outliers exist a sensitivity analysis eliminating or reducing the outlier effect may be performed and differences between their results may be reviewed, if required.

Pharmacokinetic (PK) plasma concentration data will be evaluated for outliers by visual inspection, and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practice.

8.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version [9.4] or later.

9. Statistical Methods of Analysis

9.1 General Considerations

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 study part (Part A, B and C), actual treatment received and at each protocol-specified scheduled 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.

9.2 Subject Accountability

A summary of study reporting period and analysis set dispositions will also be prepared.

Key study dates for the first subject enrolled, last subject enrolled and last subject's end of study include any other key study dates that are relevant for the study design (eg, last subject's end of investigational product, data cut-off date) will be presented.

The number and percent of subjects who were randomized, received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing, completed study, discontinued study and reasons for discontinuing will be summarized by treatment group and cohort and overall.

The number and percent of subjects randomized will be tabulated by study site.

Listings may be generated and reviewed but may not be included in the CSR.

9.3 Important Protocol Deviations

Important Protocol Deviation (IPD) categories are defined by the study team before the first subject's initial visit and updated during the IPD review meetings throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

Demographic (ie. age, age groups [< 40, >= 40, **<18, 18-64, ≥65**], sex, race, ethnicity) and baseline characteristics (height, weight, body mass index, medical history) will be summarized by cohort and actual treatment group and overall (i.e. total from all the cohorts involved in the analysis and irrespective of treatment received) using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by the combination of race.

9.5 Efficacy Analyses

Not applicable.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

Table 9.1. Safety Endpoint Summary Table

Endpoint	Statistical Analysis Methods	Sensitivity Analysis
Subject incidence of treatment-emergent adverse events (TEAEs)	Following analysis will be performed for safety analysis set by part (Part A, B and C) and actual treatment group. • Subject incidence of ▪ Fatal events by SOC/PT ▪ TEAEs leading to withdrawal from IP or other protocol-required therapies by SOC/PT ▪ TEAEs by SOC, PT and grade ▪ SAEs by SOC, PT and grade	Not Applicable
• Changes in laboratory safety tests, vital sings and 12-lead ECGs	Following analysis will be performed for SAS by part (Part A, B and C) and actual treatment group at protocol-specified scheduled visit. • Summary statistics of ▪ Change from baseline safety laboratory test results ▪ Change from baseline vital signs ▪ Changes from baseline ECG parameters	Not Applicable

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term. All adverse event tables will be summarized by actual treatment group, cohort.

The subject incidence of adverse events will be summarized for all TEAEs, SAEs, TEAEs leading to withdraw of IP, fatal adverse events, and adverse events of interest (EOIs).

Subject incidence of all TEAEs leading to withdrawal of IP, fatal adverse events, and will be tabulated by SOC and PT in descending order of frequency.

Subject incidence of TEAEs and SAEs will also be tabulated by SOC, PT, and grade.

Subject incidence of events of interest (EOIs) will also be tabulated according to the EOI search categories and preferred term if applicable. Events of interest of hypersensitivity will be identified using a narrow search/scope in standardized MedDRA query (SMQ). Immunogenicity, Injection site reactions and Nausea/vomiting will be identified using **a broad search/scope in** Amgen-defined MedDRA search strategies.

9.6.3 Laboratory Test Results

Listings of individual chemistry, hematology and urinalysis laboratory may be generated and reviewed but may not be included in the CSR. Values outside the normal laboratory reference range will be flagged as high or low at baseline and each post-baseline time point on the listings.

For key laboratory parameters which are given in Table 9.2 below, summary statistics will be provided for actual value, change from baseline and percent change from baseline by study part (Part A, B and C), actual treatment group at each protocol-specified scheduled visit.

Table 9.2. Laboratory parameters

Local Laboratory (Chemistry): Sodium, Potassium, Chloride, Bicarbonate, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Glucose, BUN or Urea, Creatinine, Uric acid, **Creatine kinase**, Total bilirubin, Direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT)
Local Laboratory (Urinalysis): Specific gravity, pH
Local Laboratory (Hematology): RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, Reticulocytes, Platelets, WBC, Differential • Eosinophils • Basophils • Lymphocytes • Monocytes • Total Neutrophil Count
Central Laboratory: Antibodies, Serum PK, Plasma PD: • Insulin • Glucose • c-peptide • Glucagon, Serum PD: •Free fatty acids, Lipid Panel[a] • HDL • LDL • Triglycerides •Cholesterol, HbA1c[a]

[a] 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; HDL = high density lipoprotein; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

9.6.4 Vital Signs

Summary statistics of heart rate and blood pressure will be provided for actual value, change from baseline and percent change from baseline by study part (Part A, B and C) and actual treatment group at each protocol-specified scheduled visit. Listings of vital signs may be generated and reviewed but may not be included in the CSR.

9.6.5 Physical Measurements

Summary statistics of physical measurements (weight, waist circumference and BMI) will be provided for actual value, change from baseline and percent change from baseline by study part (Part A, B and C) and actual treatment group at each protocol-specified scheduled visit.

9.6.6 Electrocardiogram

Summaries over time and changes from baseline over time will be provided for all 12-lead ECG parameters (QRS, QT, RR, PR, and QTcF) by study parts (Part A, B and C) and actual treatment group at each specified protocol scheduled visit.

The analysis Fridericia's (QTcF) QT correction will be performed using the derived results as specified in Section 5. Subjects will be categorized into the following groups per their maximum change from baseline in QTcF. Unscheduled assessments will be included in the determination of the maximum change.

- ≤ 30 msec

- > 30 – 60 msec
- > 60 msec

Subjects will also be categorized into the following groups per their maximum post baseline QTcF. Unscheduled assessments will be included in the determination of the maximum post baseline value.

- ≤ 450 msec
- > 450 – 480 msec
- > 480 – 500 msec
- > 500 msec

All on-study electrocardiogram (ECG) data will be listed and reviewed but may not be included in the CSR.

9.6.7 Antibody Formation

Subject incidence of developing anti-AMG 171 antibodies (binding and if positive for binding antibodies, neutralizing) at any time will be tabulated by study part (Part A, B and C) and actual treatment group.

Listings of antibody data may be generated and reviewed but may not be included in the CSR.

9.6.8 Exposure to Investigational Product

Summary statistics of number of doses of IP, total amount of the IP and the proportion of subjects receiving each dose level will be provided by study part (Part A, B and C) and actual treatment group. Subject-level data may be provided instead of the summary if the subject incidence of exposure to IP is low or single dose is given.

9.6.9 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications will be summarized by preferred term for each study part (Part A, B and C) and actual treatment group at each protocol-specified scheduled visit as coded by the World Health Organization Drug dictionary version September 2017 or later.

9.7 Other Analyses

9.7.1 Secondary Endpoint – Pharmacokinetics Analysis

The Clinical Pharmacology Modeling and Simulation (CPMS) group at Amgen will perform this part of the analysis. The analysis will be performed using the PK analysis set.

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.

9.7.2 Exploratory Endpoints

9.7.2.1 Pharmacodynamic Parameters

Summary statistics for actual values, change from baseline and percent change from baseline will be provided for the following parameters by study part (Part A, B and C), actual treatment group at each protocol-specified scheduled visit:

- The fasting and post-mixed meal challenge glucose, insulin, c-peptide, glucagon, and free fatty acid (FFA) concentrations (Part A only).
- Fasting lipid levels, including, but not limited to, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides
- HbA1c levels (**Part B only**).
- Body composition parameters (eg. Fat, muscle and bone mineral content) measured by Dual-energy x-ray absorptiometry (**Part B only**).

Graphs of mean percent change from baseline by study part (Part A, B and C), actual treatment group at each protocol-specified scheduled visit will be provided for all pharmacodynamic parameters.

10. Changes From Protocol-specified Analyses

No PK and pharmacodynamic (PD) analysis will be performed for gastric emptying test. PD analysis set will also not be created.

11. Literature Citations / References

12. Prioritization of Analyses

There is no prioritization of analyses.

13. Data Not Covered by This Plan

Not applicable.

14. Appendices

Appendix A. Handling of Missing or Incomplete Dates

Adverse event and concomitant medication records with completely or partially missing start dates will be imputed as described in Table below.

		Stop Date						
		Complete: yyyymmdd		Partial: yyyymm		Partial: yyyy		Missing
Start Date		<1st Dose	≥1st Dose	<1st Dose yyyymm	≥1st Dose yyyymm	<1st Dose yyyy	≥1st Dose yyyy	
Partial: yyyymm	Equal to 1st Dose yyyymm	2	1	2	1	N/A	1	1
	Not equal to 1st Dose yyyymm		2		2	2	2	2
Partial: yyyy	Equal to 1st Dose yyyy	3	1	3	1	N/A	1	1
	Not equal to 1st Dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute the date of first dose
2 = Impute the first of the month
3 = Impute January 1 of the year
4 = Impute January 1 of the stop year

Note: For subjects who were never treated (first dose date is missing), partial start dates will be set to the first day of the partial month.
Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.