Statistical Analysis Plan

Protocol Title:	A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 133 in Subjects With Obesity
Short Protocol Title:	Single and Multiple Ascending Dose Study of AMG 133 in Subjects with Obesity
Protocol Number:	20180048
NCT Number:	NCT04478708
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SAP Date:	**Document Version** — **Date** **Original (v1.0)** — 17 September 2020 **Amendment (v2.0)** — 29 July 2021 **Amendment (v3.0)** — 15 February 2021 **Amendment (v4.0)** — **28 October 2022**

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	17 September 2020	Original version for approved protocol
Amendment 1 (v2.0)	29 July 2021	The following changes were made in version 2.0 of the SAP to align with Protocol Amendment 3: 1. Section 2 *Objectives, Endpoints and Hypotheses* was updated to include the MAD group and analyze immunogenicity of AMG 133, [redacted] 2. Section 3 *Study Overview* was updated to include study phases Part A (cohorts 1-6, 11) and Part B (cohorts 7-10). [redacted] were added to Part B. 3. Section 5 *Definitions* was updated to include baseline [redacted], subject-level EOS, study EOS, IP exposure, study exposure, primary completion, and IA cut-off date definitions; removed QTcB 4. Section 6 *Analysis Set* was updated for the definition of Full Analysis Set and Interim Analysis Set 5. Section 7 *Planned Analyses* was updated where a planned administrative interim analysis was added and details for the interim and final analyses included. 6. Section 8.3 *Handling of Missing and Incomplete Data* was updated to clarify that only a partially missing start date will be imputed and [redacted] 7. Section 9.1 *General Considerations* was updated to include more details on the way the data will be presented and summarized by

		study phase and actual treatment group. Any other related sections were also updated. 8. Section 9.4 Demographics and Baseline Characteristics was updated to include waist circumference and correct typo on 'randomized' 9. Section 9.6 *Safety Analyses* was updated to remove grade in the analysis summary and treatment related TEAEs 10. Section 9.6.2 *Adverse Events* was updated to include more details on the way the data will be presented and summarized. EOIs were also updated for the same. 11. Section 9.6.3 *Laboratory Test Results* was updated to remove lab parameters that were only assessed during screening and baseline; PD, PK, and antibody parameters were removed due to inclusion elsewhere. Safety assessments were added. 12. Section 9.6.4 *Vital Signs* was updated to remove respiratory rate and temperature to be consistent with Protocol Amendment 3 13. Section 9.6.5 *Physical Measurements* was updated to include summary of waist circumference and plots of weight over time 14. Section 9.6.6 *Electrocardiogram* was updated with correct ECG parameters; listings and plots was updated with more details 15. Section 9.6.7 *Antibody Formation* was updated to include anti-GLP1 16. Section 9.7.1 *Secondary Endpoint - Pharmacokinetic Analysis* was updated to include

		power model to be consistent with Protocol Amendment 3 17. [redacted] was added to be consistent with Protocol Amendment 3 18. [redacted] was added to be consistent with Protocol Amendment 3 19. [redacted] was added to be consistent with Protocol Amendment 3 20. [redacted] was added to be consistent with Protocol Amendment 3 21. [redacted] was added to be consistent with Protocol Amendment 3 22. [redacted] was added to be consistent with Protocol Amendment 3 23. [redacted] was added to be consistent with Protocol Amendment 3 24. Section 10 *Changes From Protocol-specified Analyses* was updated to clarify no added plans for COVID-19 impact analyses. 25. Section 11 *Literature Citations / References* was updated 26. Section 13 *Data Not Covered by This Plan* was updated to clarify exploratory endpoints not analyzed under this plan 27. Appendix A. *Handling of Missing or Incomplete Dates* was updated to

		clarify that only a partially missing start date will be imputed
Amendment 2 (v3.0)	15 February 2022	The following changes were made in version 3.0 of the SAP to align with Protocol Amendment 4: 1. Section 2 *Objectives, Endpoints and Hypotheses* was updated to add Part C (cohorts 12 and 13) an open-labeled modified dose-escalation MAD cohorts 2. Section 3 *Study Overview* was updated to add language and flexibility to cohorts 10 and 11 enrollment. Included Part C (cohorts 12 and 13) and updated texts around study design, sample size calculations, and rows in Table 3-1 Planned Dose Levels by Cohort. 3. Section 5 *Definitions* was updated to define second interim analysis cutoff date 4. Section 7.1 *Interim Analysis and Early Stopping Guideline* was updated to include second interim analysis 5. Section 7.3 *Final Analysis* was updated to clarify cohorts 1 to 13 will be included 6. Section 9 *Statistical Methods of Analysis* was updated throughout to clarify dose phase indicates SAD cohorts (Part A) and MAD cohorts (Parts B and C) 7. Section 9.6.3 *Laboratory Test Results* was updated to provide clarifying language surrounding laboratory tests in Table 9.2 Laboratory Parameters. Clarified abnormal lab listings may be provided. 8. Section 9.6.7 *Antibody Formation* was updated to align with protocol to include anti-AMG 133 and neutralizing to native GLP-1 tests.

		9. [redacted] 10. 11. Section 10. *Changes From Protocol-specified Analyses* was updated that AEs will not be tabulated by relationship to study drug 12. Made formatting and editorial changes throughout the SAP.
Amendment 3 (v4.0)	**28 October 2022**	**The following changes were made in version 4.0 of the SAP to streamline analysis to key parameters and time-points:** **1. Section 9.6.3 Laboratory Test Results removed calcium and nucleated red blood cells in Table 9-2. Laboratory Parameter.** **2. Table 9-7 updated to remove the correlation analysis for some parameters related to [redacted] and physical measurements for different time-points.**

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[redacted]

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
ADA	Antidrug antibodies
ADPC	Analysis dataset for PK concentrations
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
BUN	Blood urea nitrogen
CK	Creatine kinase
Cmax	Maximum observed drug concentration during a dosing interval
CPMS	Clinical Pharmacology Modeling and Simulation
CRP	C-reactive protein
CRP-HS	C-reactive protein-high sensitivity
CSR	Clinical study report
[redacted]	
DLRM	Dose level review meeting
DLRT	Dose level review team
[redacted]	
ECG	Electrocardiogram
EOI	Event of interest
EOS	End of study
FAS	Full analysis set
[redacted]	
GLP-1	Glucagon-like peptide-1
[redacted]	
HLT	High level term
IP	Investigational product
IPD	Important protocol deviation
IV	Intravenous

LDH	Lactate dehydrogenase
[redacted]	
LLQ	Lower limit of quantification
LOESS	Locally estimated scatterplot smoothing
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
PD	Pharmacodynamic(s)
PDAS	Pharmacodynamic analysis set
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic analysis set
PR	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.
PT	Preferred term
QW	Every week
Q4W	Every four weeks
QRS	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	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
QTcF	Fridericia-corrected QT Interval
RBC	Red blood cell count
RDW	Red cell distribution width
[redacted]	
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous

SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment emergent adverse event
tmax	Time of maximum observed concentration
WBC	White blood cell count

1. Introduction

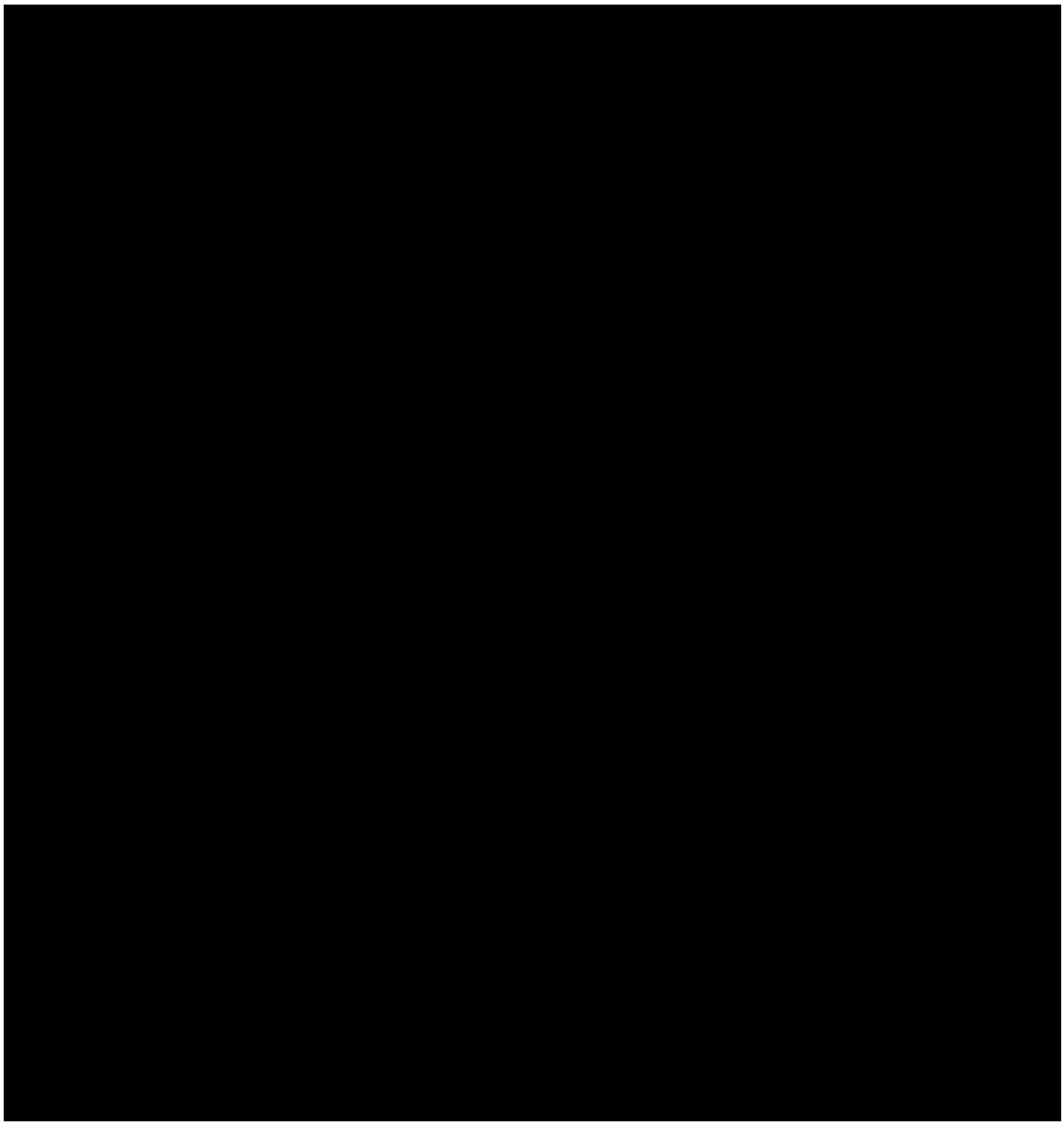
The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20180048, AMG 133 dated 03 February 2022. The scope of this plan includes interim analyses and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints/Estimands

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

Exploratory
[redacted]



2.2 Hypotheses and/or Estimations

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

3. Study Overview

3.1 Study Design

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

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

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

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

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

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

The DLRT for SAD cohort 11 will also make dosing recommendations for cohort 9. [redacted]

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

The dose recommended for cohort 10 will depend on the final dose recommended for cohort 9 and the safety and tolerability profiles for MAD cohorts 7 and 8. [redacted]

[redacted]

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

Part C (cohort 12 to 13) is an open-label modified dose-escalation MAD study in subjects with obesity. Doses selected for these cohorts have been doses previously studied in Part A and Part B and have been shown to have an acceptable safety and tolerability profile. Doses selected in Part C will not exceed the dose levels previously studied in the MAD cohorts (420 mg SC Q4W x 3). Cohort 12 will receive [redacted] mg SC on days [redacted] followed by [redacted] mg SC on days [redacted]. Cohort 13 will receive [redacted] mg SC on days [redacted] followed by [redacted] mg SC on days [redacted]. Up to 6 subjects per cohort will receive AMG 133. Cohort 12 and cohort 13 will enroll in parallel. The DLRT will review the safety and laboratory data through at least day 36.

- MAD cohorts 7 to 9: Study drug will be administered 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 the SAD phase (Part A). Three different dose levels will be evaluated with the lowest dose administered to cohort 7, and 2 higher ascending doses administered to cohorts 8 and 9. The dose level for cohorts 7 to 9 will not exceed the highest dose evaluated in cohorts 1 to 6 and cohort 11 (Part A). Subjects enrolled in cohorts 7 to 9 will also be asked to [redacted].
- MAD cohort 10: Up to twenty subjects will be randomized in a 3:1 ratio to receive AMG 133 or placebo SC. All subjects will be asked to use [redacted] The dose level will not exceed the highest dose evaluated in cohorts 7 to 9 (Part B).

Table 3-1. Planned Dose Levels by Cohort

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

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

Dose Level Review Meetings

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

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

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

3.2 Sample Size

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

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

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 the randomized treatment group unless more doses of the other treatment (placebo or AMG 133) are received than 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:

A TEAE is any AE that is categorized as an AE starting on or after first dose of investigational product (IP) as determined by the flag indicating if the AE started prior to the first dose on the Events case report form and up to the end of study date.

Baseline:

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

Baseline ECG Parameters:

Baseline ECG will be calculated as the average of the available pre-dose 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.

[redacted]

Change from Baseline:

The arithmetic difference between a post-baseline value and the baseline value from a given variable at a given time point is defined as:
Change from baseline = (post-baseline value at given time point – 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 at given time point – baseline value] / baseline value) × 100.

Investigational Product:

The IPs are defined as AMG 133 or placebo.

Subject-level End of Study 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.

Study End Date:

The study end date is the last end of study (EOS) date of all randomized subjects.

Primary Completion:

The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoints.

If the study concludes prior to the primary completion date originally planned in the protocol (i.e., 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 (i.e., last subject last visit).

Study Day 1:

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

Study Day:

For each subject and a given date of interest, study day is defined as the number of days since Study Day 1:
Study Day = (date of interest – Study Day 1 date) + 1.
If the date of interest is prior to the Study Day 1:
Study Day = (date of interest – Study Day 1 date).

IP Exposure Period in Weeks

For subjects dosed with IP:
(Last Dose Date of IP – date of Study Day 1 + 1) / 7

Study Exposure Period in Weeks

For each randomized subject:
(EOS Date – Randomization Date + 1) / 7

Fridericia-corrected QT Interval:

The Fridericia-corrected QT interval (QTcF) will be calculated from the investigator reported QT (msec) and RR interval (msec), as follows: $QTcF=QT / (RR/1000)^{1/3}$.

Data Cutoff Date for Interim Analysis:

The first interim analysis data cutoff date will be approximately 36 days after cohort 9 enrollment. The second interim analysis data cutoff date will be after all subjects in cohorts 1 to 11 have completed the study.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set (FAS) will consist of all randomized subjects who receive at least one dose of IP.

6.2 Safety Analysis Set

The safety analysis set is the same as the FAS

6.3 Pharmacokinetic Analyses Set(s)

The pharmacokinetics analysis set (PKAS) will consist of all subjects who receive at least one dose of AMG 133 for whom at least one concentration post-dose or PK parameter or endpoint can be adequately estimated.

6.4 Interim Analyses Set(s)

The interim analysis set will be an interim version of the FAS which will consist of all observations that have occurred up to the cutoff date for the interim analysis. Refer to Section 7.1 for details of the interim analysis.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

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

The first administrative interim analysis will be conducted after the DLRM for cohort 9 with no preplanned adaptive decisions. The objective of the interim analysis is to obtain preliminary information for planning subsequent trials. This analysis will include data from cohorts 1 to 9. If cohort 10 and 11 has undergone DLRM prior to the DLRM for cohort 9, data from these cohorts may be included in the analysis as well. For the first interim analysis, the data cutoff is 36 days after the last subject in cohort 9 is enrolled. At that time, the database will be cleaned, processed, and a snapshot for cohorts 1 to 9 and, if applicable, an “as is” snapshot for cohorts 10 and 11 will be taken.

The analysis performed at the first interim analysis will include:

- Assessment of the primary endpoints:
  - subject incidence of TEAEs

  - changes in laboratory safety test (see Table 9-2)
  - changes in vital signs
  - changes in 12-lead ECGs

- Assessment of the secondary endpoints:
  - PK parameters
  - incidence of antidrug antibodies (ADA)

- Assessment of the exploratory endpoints:
  - [redacted]

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

7.2 Primary Analysis

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

7.3 Final Analysis

The final analysis will occur after all subjects in cohort 1 to 13 have completed this study. Data will be locked prior to conducting the final analysis based on a clean snapshot of data from cohorts 1 to 13.

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

For the interim and final analyses, the Amgen Global Study Operations-Data Management department will provide all data to be used in the planned analyses, except as indicated below for the Analysis Dataset for PK Concentrations (ADPC). This study will use the RAVE database.

The ADPC will be provided to Clinical Pharmacology Modeling and Simulation (CPMS) from Global Statistical Programming.

8.3 Handling of Missing and Incomplete 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 the line listings, as applicable.

[redacted]

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

AE and concomitant medication with completely or partially missing dates will be queried. If the date is still incomplete with year only or year and month only after the query (i.e., partially missing date information), the start date will be imputed as described in Appendix A.

[redacted]

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 by the use of descriptive statistics. All data confirmed as an outlier will not be excluded in the interim or final analyses described in this SAP.

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.

PK plasma concentration data will be evaluated for outliers by visual inspection, and decision to re-assay individual samples will be made in accordance with standard PK 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 Statistical Analysis Software System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

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

Descriptive statistics on continuous measurements will include means, medians, 25th and 75th percentiles, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. PK, PD, and clinical laboratory data will be summarized by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group at each protocol-specified scheduled visit.

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

Data for subjects receiving placebo will be combined across cohorts 7 to 9 and cohorts 12 to 13 within Parts B to C and data for subjects receiving placebo from cohort 10 will be summarized separately.

Data for subjects receiving AMG 133 will be presented separately by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group. 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 included any other key study dates that are relevant for the study design (e.g., last subject's end of IP, data cutoff date) will be presented.

The number and percent of subjects who were randomized, received IP, completed IP, discontinued IP and reason for discontinuing, completed study, discontinued study and reason for discontinuing will be summarized by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group.

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 clinical study report (CSR).

9.3 Important Protocol Deviations

IPDs categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews 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 (i.e., age, age groups [<40, >=40], sex, race, ethnicity) and baseline characteristics (height, weight, waist circumference, BMI, medical history) will be summarized by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C), actual treatment group and overall (i.e., total from all the cohorts involved in the analysis and irrespective of the randomized treatment) 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)

A table summarizing the primary endpoints and planned analysis methods is shown below:

Table 9-1. Primary Endpoint Summary Table

Endpoint	Statistical Analysis Method	Sensitivity Analysis
Subject incidence of TEAEs	The following analyses will be performed on the FAS and summarized by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group. Subject incidence tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT) of • TEAEs • fatal AEs • serious adverse events (SAEs) • AEs leading to withdrawal from IP or other protocol-required therapies	None
Changes in laboratory safety tests, vital signs and 12-lead ECGs	The following analyses will be performed on the FAS and summarized by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group at protocol-specified scheduled visit. Summary statistics of • change from baseline safety laboratory test results	None

	• change from baseline vital signs • change from baseline ECG parameters	

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 AEs to SOC, HLT, and PT. All AE tables will be summarized by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group.

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

Subject incidence of all TEAEs, SAEs, TEAE's leading to withdrawal of IP, and fatal AEs will be tabulated by SOC, HLT, and PT in descending order frequency.

Subject incidence of EOIs will also be summarized according EOI search categories and PT if applicable. Nausea and vomiting are identified using a broad search scope in a standardized MedDRA query (SMQ) of gastrointestinal nonspecific inflammation and dysfunctional conditions. Hypersensitivity is identified using a narrow search scope in SMQ. Immunogenicity and injection site reactions are identified using a broad search scope in Amgen-defined MedDRA search strategies.

9.6.3 Laboratory Test Results

Abnormal lab 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 Table 9-2 below, summary statistics will be provided for actual value, change from baseline and percentage change from baseline by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group at each protocol-specified scheduled visit.

Table 9-2. Laboratory Parameters

Local Laboratory (Chemistry): sodium, potassium, chloride, bicarbonate, total protein, albumin, adjusted calcium, magnesium, phosphorus, BUN or urea, creatinine, uric acid, total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), CRP (cohort 10), CRP-HS (cohorts 7 to 9 and cohorts 12 to 13), amylase, lipase, CK
Local Laboratory (Urinalysis): specific gravity, pH
Local Laboratory (Hematology): RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, reticulocytes, platelets, WBC total WBC Differential: eosinophils, basophils, lymphocytes, monocytes, total neutrophil count[a]
Central Laboratory (Other Labs): [redacted]

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

[redacted]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; [redacted]ve protein; CRP-HS = C-reactive protein-high sensitivity; [redacted] CK = creatine kinase; [redacted] MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; [redacted] 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

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 dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to 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 body weight and BMI will be provided for actual value, change from baseline, and percent change from baseline by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group at each protocol-specified scheduled visit. For Parts B to C (cohorts 7 to 10 and cohorts 12 to 13), [redacted] In addition, graphs of mean percent change from baseline by dose

phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group at each protocol-specified scheduled visit will be provided for weight.

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 dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group at each protocol-specified scheduled visit.

The analysis QTcF QT correction will be performed using the derived results as defined 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 ECG data will be listed for selected parameters of interest; these results will be reviewed but may not be included in the CSR.

9.6.7 Antibody Formation

Subject incidence of developing anti-AMG 133 antibodies (binding and if positive, neutralizing to native GLP-1, when available) at any time will be tabulated by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to 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 IP, and proportion of subjects receiving each dose level will be provided by dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to 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 only a single dose is given.

9.6.9 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications will be summarized by PT for each dose phase (SAD cohorts in Part A and MAD cohorts in Parts B to C) and actual treatment group as coded by the World Health Organization Drug dictionary version September 2017 or later.

9.7 Analyses of Secondary and Exploratory Endpoints

9.7.1 Secondary Endpoint — Pharmacokinetics Analysis

The PK analysis will be performed by Amgen CPMS department; analyses will be performed using the PKAS.

Plasma AMG 133 concentrations will be determined using a validated assay. Individual plasma concentration-time plots for AMG 133 will be presented for each subject as well as mean concentration-time plots for each dose cohort. PK parameters that may include, but are not limited to AUC, C_{max}, and t_{max} will be estimated using either compartmental (e.g., PK modeling) or non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters.

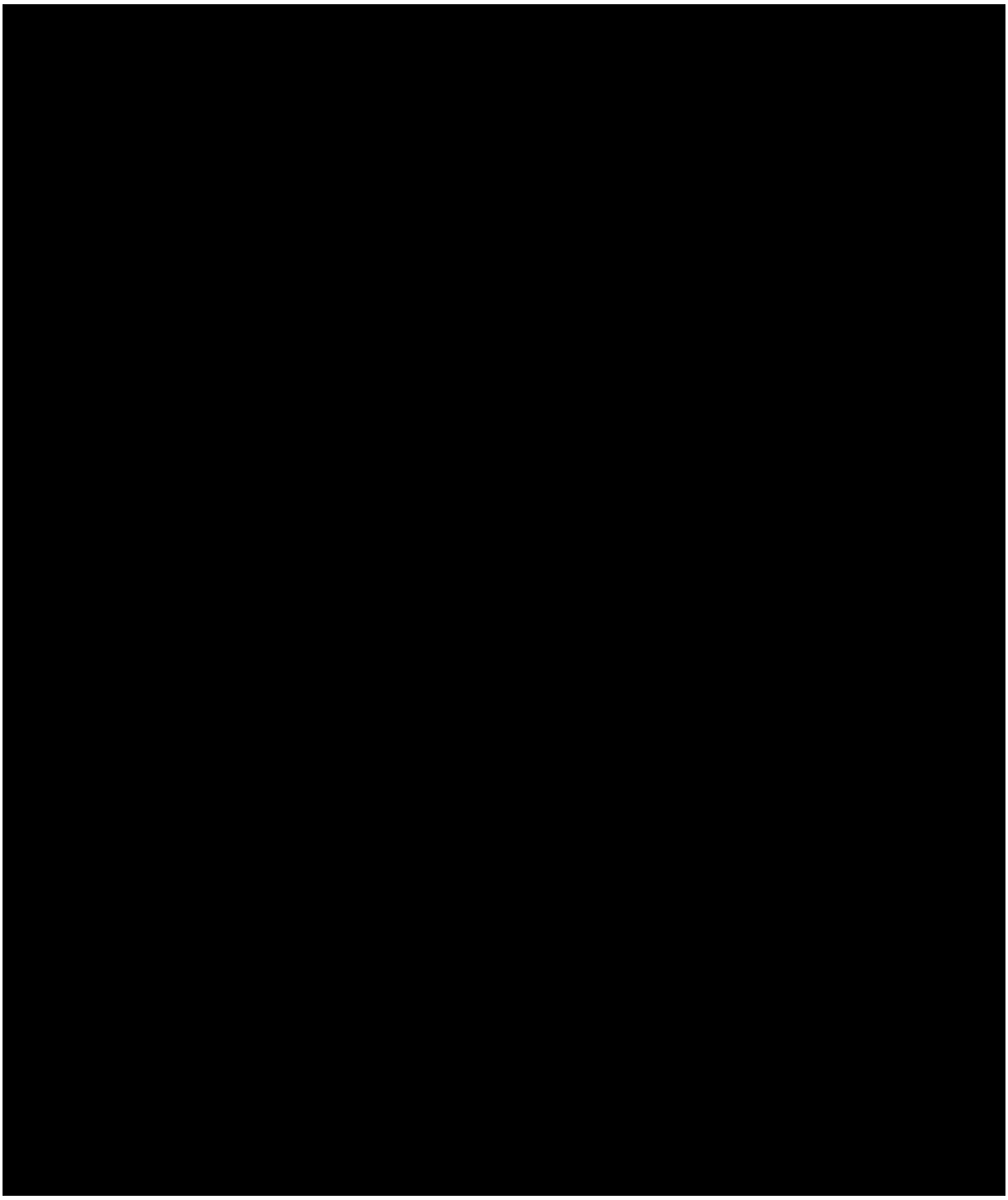
Actual dosing and sampling time will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter for each dose cohort.
A power model will be used to examine dose/concentration relationship over the SC cohorts. The dependent variable will be ln(AUC) or $\log_e$(Cmax) and the independent variable will be $\log_{e(}$dose).

[redacted]

9.7.2 Exploratory Endpoints

[redacted]

[redacted]



[redacted]

10. Changes From Protocol-specified Analyses

There are no planned COVID-19 impact analyses. AEs will not be tabulated by relationship to study drug.

11. Literature Citations / References

Metzger JS, et al. Patterns of objectively measured physical activity in the United States. *Med Sci Sports Exerc.* 2008; 40(4):630-810.

Tudor-Locke C, et al. A catalog of rules, variables, and definitions applied to accelerometer data in the National Health and Nutrition Examination Survey, 2003-2006. *Prev Chronic Dis*. 2012; 9:E113.

12. Prioritization of Analyses

There is no prioritization of analysis.

13. Data Not Covered by This Plan

This SAP does not address the analyses for the exploratory objectives

14. Appendices

Appendix A. Handling of Missing or Incomplete Dates

AE and concomitant medication records with partially missing start dates will be imputed as described in the table below.

Start Date		Stop Date: Complete: *yyyymmdd*		Stop Date: Partial: *yyyymm*		Stop Date: Partial: *yyyy*		Stop Date: Missing
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	
Partial: *yyyymm*	**= 1st dose *yyyymm***	2	1	n/a	1	n/a	1	1
	≠ 1st dose *yyyymm*		2	2	2	2	2	2
Partial: *yyyy*	**= 1st dose *yyyy***	3	1	3	1	n/a	1	1
	≠ 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 or first day of year if month is also missing. If the start date imputation leads to a start date that is after the stop date, then the start date will not be imputed.