Statistical Analysis Plan

Protocol Title:	**A Phase 1b, Randomized, Double-blind, Placebo-controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 598 in Obese Subjects**
Short Protocol Title:	Multiple Ascending Dose Study of AMG 598 in Obese Subjects
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Table of Contents

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
CI	confidence interval
C_{max}	maximum serum concentration
DLRM	Dose level review meeting
DXA	Dual-energy x ray absorptiometry
CTCAE	Common Terminology Criteria for Adverse Events
ECG	12-lead electrocardiogram
eCRF	electronic case report form
EOS	End of Study
FFA	Free fatty acid
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagone-like peptide-1
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HR	heart rate
IP	investigational product
IPD	important protocol deviation
LDL-C	low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed meal tolerance test
PD	pharmacodynamic(s)
PI	Principle investigator
PK	pharmacokinetic(s)
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
RR	respiratory rate
SAE	serious adverse event

Abbreviation or Term	Definition/Explanation
SC	Subcutaneous
TEAE	Treatment emergent adverse event
t_{max}	time to maximum serum concentration

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 3 for study 20170139, AMG 598 dated 25 June 2019. 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 multiple subcutaneous (SC) doses of AMG 598 administered alone or in combination with liraglutide in subjects with obesity	• Subject incidence of treatment-emergent adverse events • Safety laboratory data, vital signs, and electrocardiograms (ECGs)
Secondary	
• To characterize the PK of multiple SC doses of AMG 598 administered alone or in combination with liraglutide in subjects with obesity	• AMG 598 PK parameters may include, but are not limited to, maximum observed concentration (Cmax), time of maximum observed concentration (tmax), and area under the concentration time curve (AUC)
Exploratory	
• To characterize the PD effects of AMG 598	PD parameters: o Concentrations of fasting glucose, insulin, c-peptide, glucose dependent insulinotropic polypeptide (GIP), glucagon-like polypeptide type 1 (GLP-1), glucagon, and free fatty acid (FFA) o Concentration-time profiles and AUC for metabolic parameters following a mixed meal tolerance test (MMTT) o Lipid levels, including but not limited to, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides o Hemoglobin A1c (HbA1c) o Potential biomarkers including, but not limited to inflammatory and adipose tissue markers

Objectives	Endpoints
• To assess the effects of AMG 598 on body weight, waist circumference and body mass index (BMI)	• Change in body weight, waist circumference, and BMI
• To assess the effect of AMG 598 on bone mineral density by dual energy x-ray absorptiometry (DXA) (cohorts 1-6)	• Changes in bone mineral density as measured by DXA (cohorts 1-6)
• To assess the effect of AMG 598 on body composition (cohort 7)	• Changes in body composition as measured by whole body DXA (cohort 7)
• To evaluate the immunogenicity of AMG 598	• Incidence of anti-AMG 598 antibody formation

2.2 Hypotheses and/or Estimations

- AMG 598 will be safe and well tolerated following multiple SC dose administrations in subjects with obesity across the dose range evaluated
- AMG 598 in combination with liraglutide will be safe and well tolerated following multiple SC dose administrations in subjects with obesity across the dose range evaluated
- AMG 598 PK profile following multiple SC dose administrations will support selection of dose and frequency of administration in future multi-dose trials of AMG 598

3. Study Overview

3.1 Study Design

This is a randomized, placebo-controlled, double-blind, multiple ascending dose study in subjects with obesity. The study consists of a total of 7 cohorts; 3 cohorts (1, 3 and 5) with administration of AMG 598 or matching placebo SC every 4 weeks (Q4W) x3, 3 cohorts (2, 4 and 6) with Q4W x3 SC administration of AMG 598 or matching placebo in combination with liraglutide SC once daily (QD) ascending doses, and 1 cohort (cohort 7) with SC administration of AMG 598 or matching placebo SC Q4W x3 in addition to liraglutide (3.0 mg SC QD) in subjects who have been on a stable dose of liraglutide (3.0 mg SC QD) for at least 6 months. In cohorts 1-6, eight (8) subjects will be randomized to receive AMG 598 or placebo SC in a 3:1 ratio as described in the table below. In cohort 7, sixty (60) subjects will be randomized in a 1:1 ratio to receive AMG 598 or placebo SC as described in the table below.

Planned Dose Levels by Cohort

Cohort	# Subjects	Product	Dose/ Frequency	Route	N (active: placebo)
1	8	AMG 598/Placebo	70 mg Q4W x 3	SC	6:2
2	8	AMG 598/Placebo + Liraglutide	70 mg Q4W x 3 + 0.6, 1.2, 1.8, 2.4, 3.0 mg QD[a]	SC SC	6:2
3	8	AMG 598/Placebo	210 mg Q4W x 3	SC	6:2
4	8	AMG 598/Placebo + Liraglutide	210 mg Q4W x 3 + 0.6, 1.2, 1.8, 2.4, 3.0 mg QD[a]	SC SC	6:2
5	8	AMG 598/Placebo	420 mg Q4W x 3	SC	6:2
6	8	AMG 598/Placebo + Liraglutide	420 mg Q4W x 3 + 0.6, 1.2, 1.8, 2.4, 3.0 mg QD[a]	SC SC	6:2
7	60	AMG 598/Placebo + Liraglutide	420 mg SC Q4W x 3 based on the safety, PK and PD from cohorts 1– 6 + 3.0 mg QD[b]	SC	30:30

[a] Subjects will start the first dose of liraglutide (0.6 mg, SC QD) on day 1, and increase the dose of liraglutide by 0.6 mg dose increment every 7 days, up to the full dosage of 3.0 mg by week 5 and remain on 3.0 mg until day 84, inclusive

[b] Subjects eligible for the study will have been on a stable dose of liraglutide 3.0 mg SC QD for at least 6 months and will continue liraglutide 3.0 mg SC QD throughout the screening and study period from study days -56 to end of study (EOS) (day 207)

A dose level review meeting (DLRM) will be held to review the data and monitor safety before escalation to the next higher dose or expansion to the liraglutide combination cohort. The DLRM members will be composed of, at minimum, the investigator(s) actively enrolling subjects (whether in screening or enrolled) at the time of the meeting, the Amgen Medical Monitor, and Amgen Global Safety Officer or designee, and Amgen Study Manager or designee. Additional members may be added as needed (eg, PK/biomarker scientist, Biostatistician, or others providing expanded expertise).

The DLRM voting members include the principal investigator(s) or designee, Amgen Medical Monitor and Amgen Global Safety Officer or designee.

Escalation to a higher dose cohort or expansion to liraglutide combination cohorts 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 36 for a

minimum of 6 of the 8 subjects dosed, and upon unanimous recommendation at the Dose Level Review Meeting (DLRM). The dose level for cohort 7 will be chosen based on the preceding cohorts' safety and PK data. The dose level for cohort 7 will not exceed the highest dose evaluated in cohorts 1-6. The planned dose escalation schedule may be modified based on treatment-emergent data (safety and/or PK). Dose adjustments (if any) will be made on a treatment cohort and not on an individual subject basis and will be agreed upon by Amgen in conjunction with the Principal Investigator. Clear stopping rules will be followed, and ad hoc DLRMs will be held, if necessary.

Enrollment can be initiated in the subsequent cohorts after the planned DLRMs. The DLRMs will take place at the following time points:

DLRM #1: After a minimum of 6 out of 8 subjects dosed in cohort 1 complete study day 36. Enrollment in cohorts 2 and 3 can be initiated after DLRM #1.

DLRM #2: After a minimum of 6 out of 8 subjects dosed in each cohort 2 and 3 complete study day 36. Enrollment in cohorts 4 and 5 can be initiated after DLRM #2.

DLRM #3: After a minimum of 6 out of 8 subjects dosed in each cohort 4 and 5 complete study day 36. Enrollment in cohort 6 can be initiated after DLRM #3.

DLRM #4: After a minimum of 6 out of 8 subjects dosed in cohort 6 complete study day 36. Enrollment in cohort 7 can be initiated after DLRM #4.

3.2 Sample Size

Approximately 108 subjects (8 per cohort, cohorts 1-6; 60 in cohort 7) will be enrolled.

The sample size for the study is based on practical considerations. For safety considerations, with up to 66 subjects receiving AMG 598 (6 subjects in each of cohorts 1-6 and 30 subjects in cohort 7), there is a 96.6% chance of detecting an adverse event with a true incidence rate of 5% or greater and a 99.9% chance of detecting an adverse event with a true incidence rate of 10%.

In cohort 7, with a sample size of 30 subjects per group, there is approximately an 80% probability of observing a mean treatment difference in percent change from baseline in body weight between AMG 598 and placebo of > 3%, assuming a true treatment difference of 5%. This assumes a standard deviation for percent change from baseline in body weight of 7% in each treatment group.

Replacement of subjects:

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

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

Age

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

Treatment-Emergent Adverse Event:

A treatment-emergent adverse event (TEAE) is any adverse event that begins or worsens after the initial dose of investigational product as determined by the flag indicating the adverse event started after the first dose on the Events case report form (CRF) and ends prior to or at end of the study.

Baseline:

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

Baseline ECG:

Baseline for ECG data is defined as the pre-dose assessments on day 1.

As per protocol, predose ECGs will be performed on 3 occasions separated by at least 30 minutes all in triplicate for a total of 9 ECGs (3 sets of triplicate ECGs) at -90, -60 and -30 minutes before investigational product administration.

Baseline will be calculated by calculating the means of each of the triplicate predose observations separately and finally establishing the mean of those 3 separate means of triplicates.

Change from Baseline:

Change from Baseline is the arithmetic difference between Post-baseline and Baseline.

Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value) /

Baseline Value] x 100

Enrollment Date:

The enrollment date is defined as the randomization date. This is scheduled to be

Day -2 for Cohorts 1, 3 and 5, and Day -1 for Cohorts 2, 4 and 6 and day -28 for cohort 7.

Investigational Product:

The term investigational product is used in reference to AMG 598 or placebo.

Non-investigational Product:

Liraglutide is the non-investigational product used in this study.

Primary Completion:

The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

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

End of Study:

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

Screening Date:

The screening date is defined as the date the informed consent is signed.

Study Day 1:

Day 1 is defined as the first day that investigational product is administered to the subject.

Study Day:

Post study day 1: study day = (study date - date of Study Day 1) + 1

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

Fridericia-corrected QT Interval (QTcF)

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

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. Analysis Sets

6.1 Safety Analysis Set

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

6.2 Pharmacokinetic (PK) Analysis Set

The PK analysis set will consist of all subjects for whom at least one PK parameter or endpoint can be adequately estimated.

6.3 Pharmacodynamic (PD) Analysis Set

The PD analysis set will consist of all subjects for whom at least one PD parameter or endpoint can be adequately estimated.

6.4 Primary Analysis set

The primary analysis set will consist of all subjects from cohort 1 to 6 who receive at least one dose of investigational product.

6.5 Final Analysis set

The final analysis set will consist of all subjects from cohort 7 who receive at least one dose of investigational product.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

DLRM members will oversee progress of the study and make recommendations relating to early closure / extension or alteration of the study based on ongoing monitoring of the study data. Refer to Section 7.4.1 and 7.4.2 of the protocol amendment 3 for further details.

7.2 Primary Analysis

The primary analysis will occur after all subjects from cohorts 1 to 6 have completed the study and it will include all subjects from cohorts 1 to 6.

Data from cohort 1 to 6 will be locked prior to primary analysis is carried out and clean snapshot data from cohort 1 to 6 will be used for primary analysis.

7.3 Final Analysis

The final analysis will occur after all subjects in cohort 7 have completed the study and it will include all subjects from cohort 7.

Data from cohort 7 will be locked prior to final analysis and clean snapshot data from cohort 7 will be used for final analysis.

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

The frequency of missing and incomplete data is expected to be low in this study and therefore, missing data will not be imputed.

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 as a part of the summary tables. There will be no imputation of clinical laboratory values below LLQ for individual subject level data in line listings.

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 treatment emergent AE, concomitant medication, drug administration etc.), imputation of dates will be carried out as per Appendix A.

8.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by listing important protocol deviations (IPD) by cohort and site. The clinical study team will identify and document the criteria for important protocol deviations.

8.5 Outliers

Details of detecting outliers can be found in the Data Management Plan (DMP) or other data management document. In addition, outliers may be identified via the use of descriptive statistics. All confirmed outlier data will be included in the analyses presented in this statistical analysis plan unless there is sufficient scientific justification to exclude them.

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 will be provided for selected demographics, safety, PK and PD endpoints. Descriptive statistics on continuous measurements will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized by treatment at each time point, as applicable. Graphical summaries of the data may also be presented.

Data for subjects receiving placebo will be combined across cohorts 1, 3 and 5 (monotherapy cohorts) and separately across cohorts 2, 4 and 6 (combination therapy cohorts). Placebo data for subjects in cohort 7 will not be combined with other cohorts.

Data for subjects receiving AMG 598 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 subject disposition and investigational and non-investigational product administration will be provided for all subjects enrolled in the study along with a summary of sites.

A summary of study reporting and analysis set dispositions will also be prepared. A subject disposition listing, noting inclusion in each analysis subset, will be provided for all subjects enrolled.

A subject listing noting duration of investigational product administration, reason for discontinuation of treatment, and reason for discontinuing study will be provided. A list of subjects screened but not enrolled (screen failures) will be provided.

A subject listing will be provided for randomization information, randomized treatment and actual treatments, including usage of liraglutide, as applicable.

9.3 Important Protocol Deviations

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. Listings of subjects with IPDs as well as those with inclusion and exclusion deviations will be provided separately.

9.4 Demographic and Baseline Characteristics

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 treatment received 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

This section is not applicable.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

The primary objective of this phase 1b study is to evaluate the safety and tolerability of AMG 598 administered alone or in combination with liraglutide in subjects with obesity. The safety analyses will include the descriptive summary of treatment emergent adverse events, laboratory data, vital signs, physical measurements and ECG data.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term. The severity of each adverse event will be graded using the clinical severity grading system provided in Appendix B.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events (SAE), adverse events leading to withdrawal of investigational product (AMG598 or Placebo) and/or non-investigational product (Liraglutide), fatal adverse events and adverse events of interest (EOI) .

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product (AMG598 or Placebo) and/or non-investigational product (Liraglutide), fatal adverse events and adverse events of interest (EOI) will be tabulated by system organ class and preferred term (in which system organ class will be ordered alphabetically and the preferred terms within each system organ class will appear in descending order of frequency).

In addition, summaries of treatment-emergent and serious adverse events by preferred term in any treatment arm will be provided in descending order of frequency.

Summaries of treatment-emergent and serious adverse events will also be tabulated by system organ class, preferred term, and grade.

The subject incidence of treatment-emergent adverse events will be summarized by actual treatment received.

Treatment related treatment emergent adverse events will be further summarized (by system organ class and preferred term) for AMG 598 and liraglutide separately.

Subject incidence of events of interest will also be summarized according to their categories and preferred term. Events of interest of hypersensitivity will be identified using a narrow search/scope in standardized MedDRA query (SMQ). Events of interest of osteoporosis/osteopenia, gastrointestinal nonspecific inflammation and dysfunctional conditions, hyperglycaemia/new onset diabetes mellitus, depression and suicide/self-injury, and peripheral neuropathy will be identified using a broad search/scope in SMQ. Immunogenicity and Injection site reactions will be identified using Amgen-defined MedDRA search strategies.

9.6.3 Laboratory Test Results

Individual chemistry, hematology and urinalysis laboratory data listings will be reviewed. Parameters that will be collected are presented in table A below.

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 the parameters that are bolded in below Table A, summary statistics including actual value, change from baseline and percent change from baseline at protocol defined visits will be summarized.

Table A:

Local Laboratory: Chemistry	Local Laboratory:	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Central Laboratory: Other
Sodium **Potassium** **Chloride** **Bicarbonate/CO 2** **Total protein** **Albumin** **Calcium** **Glucose** **BUN or Urea** **Creatinine** **Total bilirubin** **Direct bilirubin** **ALP** **AST (SGOT)** **ALT (SGPT)** TSH – screening only Calcitonin –	<u>Drug Screen</u> Benzodiazepines Barbiturates Opiates Tetrahydrocannabinol Cocaine Amphetamines Ethanol (may be performed by a breath test) <u>Viral Panel</u> Hep B surface antigen HBcAb HepCAb HCV RNA PCR(as	Specific gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial cells Bacteria Casts Crystals	**RBC** **Hemoglobin** **Hematocrit** **MCV** **MCH** **MCHC** **Platelets** **WBC Differential** **• Total Neutrophils -or- seg. Neutrophils and Bands/Stabs** **• Eosinophils** **• Basophils** **• Lymphocytes** **• Monocytes**	<u>Safety assessments</u> **P1NP** **CTX-1** <u>Lipid Panel</u> **Cholesterol (total)** **LDL-C** **HDL-C** **Triglycerides**

Local Laboratory: Chemistry	Local Laboratory:	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Central Laboratory: Other
screening only Tryptase (in the event of a suspected anaphylactic reaction) **Amylase** **Lipase**	necessary) HIV[a] <u>Reproductive</u> Serum or Urine Pregnancy FSH		<u>Coagulation</u> **PT/INR** **PTT/APTT**	

[a] HIV assessment is recommended.

ALP = alkaline phosphatase; ALT alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CTX-1 = C-terminal telopeptides of Type I collagen; GIP = Glucose dependent insulinotropic peptide; GLP-1 = Glucagon-like peptide-1; HbA1c = ; hemoglobin A1c; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; P1NP = Procollagen Type 1 N-Terminal Peptide; PT = prothrombin time; PTT/APTT = activated partial thromboplastin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; WBC = white blood cell count

9.6.4 Vital Signs

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

9.6.5 Physical Measurements

The analyses of physical measurements (weight, BMI and waist circumference) will include summary statistics at each protocol scheduled visit by cohort and by treatment.

9.6.6 Electrocardiogram

All on-study ECG data listings will be reviewed.

Each ECG will include the following measurements: QRS, QT, QTc, RR, and PR intervals. The Fridericia's (QTcF) QT correction and Bazett's (QTcB) QT correction will be computed as specified in section 5. All ECG parameters will be summarized over time and change from baseline over time will be provided.

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 be summarized. 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

9.6.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 598 antibodies (binding and if positive, neutralizing) at any time will be tabulated by cohort and by treatment.

Antibody data will be listed for each subject.

9.6.8 Exposure to Investigational Product

The number of doses of IP and the proportion of subjects receiving each dose level will be summarized using descriptive statistics.

9.6.9 Exposure to non investigational product

Descriptive statistics of the number of doses of liraglutide received by each subject will be produced for cohorts 2, 4, 6 and 7.

9.6.10 Exposure to Concomitant Medication

Number and proportion of subjects receiving concomitant medication will be summarized by preferred term for each cohort and treatment as coded by the World Health Organization Drug dictionary.

9.7 Analyses of secondary and exploratory endpoints

9.7.1 Analyses of Pharmacokinetic Endpoints

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 598 concentrations will be determined using a validated assay.

Individual serum concentration-time plots for AMG 598 will be presented for each subject as well as mean concentration-time plots for each dose cohort. PK parameters including

but not limited to AUC, Cmax and tmax 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.

Liraglutide PK concentrations will be summarized.

9.7.2 Exploratory Endpoints

9.7.2.1 Pharmacodynamic Parameters:

Absolute values, change values and percent change from baseline values will be summarized in a table for following parameters:

- fasting glucose, insulin, c-peptide, glucose dependent insulinotropic polypeptide (GIP), glucagon-like polypeptide type 1 (GLP-1), glucagon, and free fatty acid (FFA)
- Concentration-time profiles and AUC for metabolic parameters following a MMTT
- Lipid levels, including but not limited to, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides
- Hemoglobin A1c

Graph of mean percent change from baseline by visit for all treatment groups will be provided for all PD parameters.

Additionally, a subset of these parameters (glucose, insulin, C-peptide, GIP, GLP-1, glucagon, and free fatty acids) will be measured on Day -1 and Day 6 postdose (ie. post IP administration) and day 64 postdose after meals during a MMTT and for these parameters, absolute values and percent change from baseline values will be summarized by cohort and treatment.

Graph of grometric mean (+/- SE) vs. time (in minutes) for days -1, 6 and 64 will be plotted for glucose, insulin, C-peptide, GIP, GLP-1, glucagon, and free fatty acids following MMTT.

9.7.2.2 Bone Mineral Density by DXA

Summary of absolute and percent changes in bone mineral density at the lumbar spine, femoral neck and total hip, as measured by DXA, will be summarized for subjects enrolled in cohorts 1-6.

9.7.2.3 Whole Body Composition by DXA

Summary of absolute and percent change from baseline values in body composition, including measures of total bone mineral context (BMC), total fat mass, total lean mass and visceral adipose tissue (VAT), as measured by whole body DXA will be summarized for subjects in cohort 7.

9.7.2.4 Weight, Waist Circumference and BMI:

Summary of absolute and percent change from baseline values in body weight, weight circumference and BMI will be summarized.

Mean percent change from baseline in weight by visit for all treatment groups will also be graphed.

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

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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 for Adverse Events and Concomitant Medications

14.1.1 Imputation Rules for Partial or Missing Stop Dates:

If the month and year are present, impute to the last day of the month.

If only the year is present, impute December 31 of that year.

If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial.

14.1.2 Imputation Rules for Partial or Missing Start Dates:

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

Appendix B. Reference Values/Clinical Severity grading

The clinical severity grading scale is as follows:

- grade 1 = mild (e.g., asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated, or does not interfere with activity)
- grade 2 = moderate (e.g., minimal intervention indicated or interferes with activity)
- grade 3 = severe (e.g., medically significant but not immediately life-threatening, prevents daily activity, or requires treatment)
- grade 4 = life-threatening (i.e., refers to an event in which the subject was, in the view of the investigator, at risk of death at the time of the event)
- grade 5 = fatal