Title Page

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 Subjects With Obesity**
Short Protocol Title:		Multiple Ascending Dose Study of AMG 598 in Subjects with Obesity
Protocol Number:		20170139
Investigational Product:		AMG 598
Trade Name:		NA
Sponsor	**Name of Sponsor:**	Amgen, Inc.
	Address:	One Amgen Center Drive
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EudraCT Number:		Enter EudraCT Number
NCT Number:		NCT03757130
Protocol Date:		**Document Version** / **Date** **Original** 20 September 2018 **Amendment 1** 07 November 2018 **Amendment 2** 15 February 2019 **Amendment 3** 25 June 2019
Version/Date:		**Data Element Standards Version** 6.1

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Investigator's Agreement:

I have read the attached protocol entitled **A Phase 1b, Randomized, Double-blind, Placebo-controlled, Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 598 in Subjects With Obesity**, dated 25 June 2019, and agree to abide by all provisions set forth therein.

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

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

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 Subjects With Obesity

Short Protocol Title: Multiple Ascending Dose Study of AMG 598 in Subjects with Obesity

Study Phase: 1

Indication: Obesity

Rationale

The current study evaluates the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of multiple ascending doses of AMG 598 alone, and in combination with liraglutide, as a potential weight loss therapy.

Objective(s)/Endpoint(s)

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
Exploratory (continued)	
• 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

Hypotheses

- 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

Overall 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 or more. 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 Q4W x 3 + 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 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.

Number of Subjects

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

Summary of Subject Eligibility Criteria

Males and females aged 18 to 65 years (inclusive) at the time of randomization with a BMI of ≥ 30.0 and ≤ 40.0 kg/m^2. Females enrolled in cohorts 1-6 must be of non-reproductive potential.

For cohort 7, subjects must additionally have been receiving liraglutide at 3.0 mg QD, SC for at least 6 months before screening, with liraglutide being generally well tolerated per the investigator's discretion (and subjects plan to continue liraglutide 3.0 mg QD, SC).

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.4.

Treatments

Cohorts 1, 3, and 5: After completion of all pre-dose procedures on the day of dosing, subjects will receive AMG 598 (70, 210, or 420 mg) or placebo SC on days 1, 29, and 57.

Cohorts 2, 4, and 6: After completion of all pre-dose procedures on the day of dosing, subjects will receive AMG 598 (70, 210, or 420 mg) or placebo SC Q4W x3 on days 1, 29 and 57 in addition to liraglutide SC QD. 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 (See Table 3-1).

Cohort 7: Subjects that have been on a stable dose of liraglutide (3.0 mg SC QD) for at least 6 months will continue to receive liraglutide (3.0 mg SC QD) and receive one dose of placebo SC on day -28, as part of a 4-week run-in. After completion of all pre-dose procedures on the day of dosing, subjects will then receive AMG 598 420 mg or placebo SC Q4W on days 1, 29, 57 in addition to the liraglutide (3.0 mg SC QD).

Procedures

Screening:

For cohorts 1-6, after informed consent is obtained, all screening procedures and tests establishing eligibility will be performed within 28 days before first dose of AMG 598 or placebo (day 1).

Subjects in cohort 7 will be screened between days -56 and -29 from first dose of AMG 598 or placebo (day 1). Subjects who meet all the screening inclusion/exclusion criteria will be eligible to report to the research facility on day -28, subjects enrolled will receive a dose of placebo.

Day -2:

Cohorts 1, 3, and 5: Subjects who meet all the screening inclusion/exclusion criteria will be eligible to report to the research facility on day -2, at which time assessments will be performed to confirm eligibility. If subjects are eligible after the completion of all day -2 study assessments, subjects will be randomized to receive either AMG 598 or placebo.

Day -1:

Cohorts 1, 3, and 5: A mixed meal tolerance test (MMTT) will be performed.
Cohorts 2, 4, and 6: Subjects who meet all the screening inclusion/exclusion criteria will be eligible to report to the research facility on day -1, at which time assessments will be performed to confirm eligibility. If subjects are eligible after the completion of all day -1 assessments, subjects will be randomized to receive either AMG 598 or placebo.

Treatment and Follow-up (day 1 to day 206):

AMG 598 or placebo will be administered SC Q4W x3 on days 1, 29 and 57 after pre-dose procedures. All procedures on day of dosing as outlined in the Schedule of Activities should occur prior to dosing of AMG 598 or placebo.

Cohorts 1, 3, and 5: Subjects will be admitted for overnight stays prior to MMTTs. An MMTT will occur on day -1, day 6 (+/- 1 day), and day 64 (+/- 1 day).

Cohorts 2, 4, and 6: Subjects may be admitted for optional overnight stays on day -1, day 6 (+/- 1 day), and day 62 (+/- 1 day).

Subjects will return to the research facility as outlined in the Schedule of Activities and will undergo the following assessments at specified time points throughout the study: clinical laboratory evaluations, adverse event (AE) and serious adverse event (SAE) collection, vital sign measurements, 12-lead ECGs, physical examinations, MMTTs, Patient Health Questionnaire (PHQ-9), Columbia Suicide Severity Rating Scale (C-SSRS), dual-energy x-ray absorptiometry (DXA) bone density measurements (cohorts 1-6) and body composition assessments (cohort 7), PK, and PD assessments. Subjects will remain in the research facility until completion of all study procedures on each visit day.

Day 207/End of Study (EOS):

Subjects will be followed through the completion of EOS procedures on day 207.

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

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1 to Table 2-3.

Statistical Considerations

Descriptive statistics will be provided for selected demographics, safety, PK and PD data. Data for subjects receiving placebo will be combined across the monotherapy cohorts and across the combination therapy cohorts.

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 at each time point when samples are collected.

The number and percentage of subjects reporting any treatment-emergent adverse events will be tabulated by system organ class and preferred term and will be further classified by relationship to treatment. SAEs and clinically significant changes in clinical laboratory test values, ECG, or vital signs will be noted. Both exploratory graphical and model-based PK/PD analyses may be conducted with selected PD markers.

The sample size for the study is based on practical considerations. For safety considerations, with up to 66 subjects receiving AMG 598, 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%.

Cohort 7 with 30:30 randomization will allow for 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%

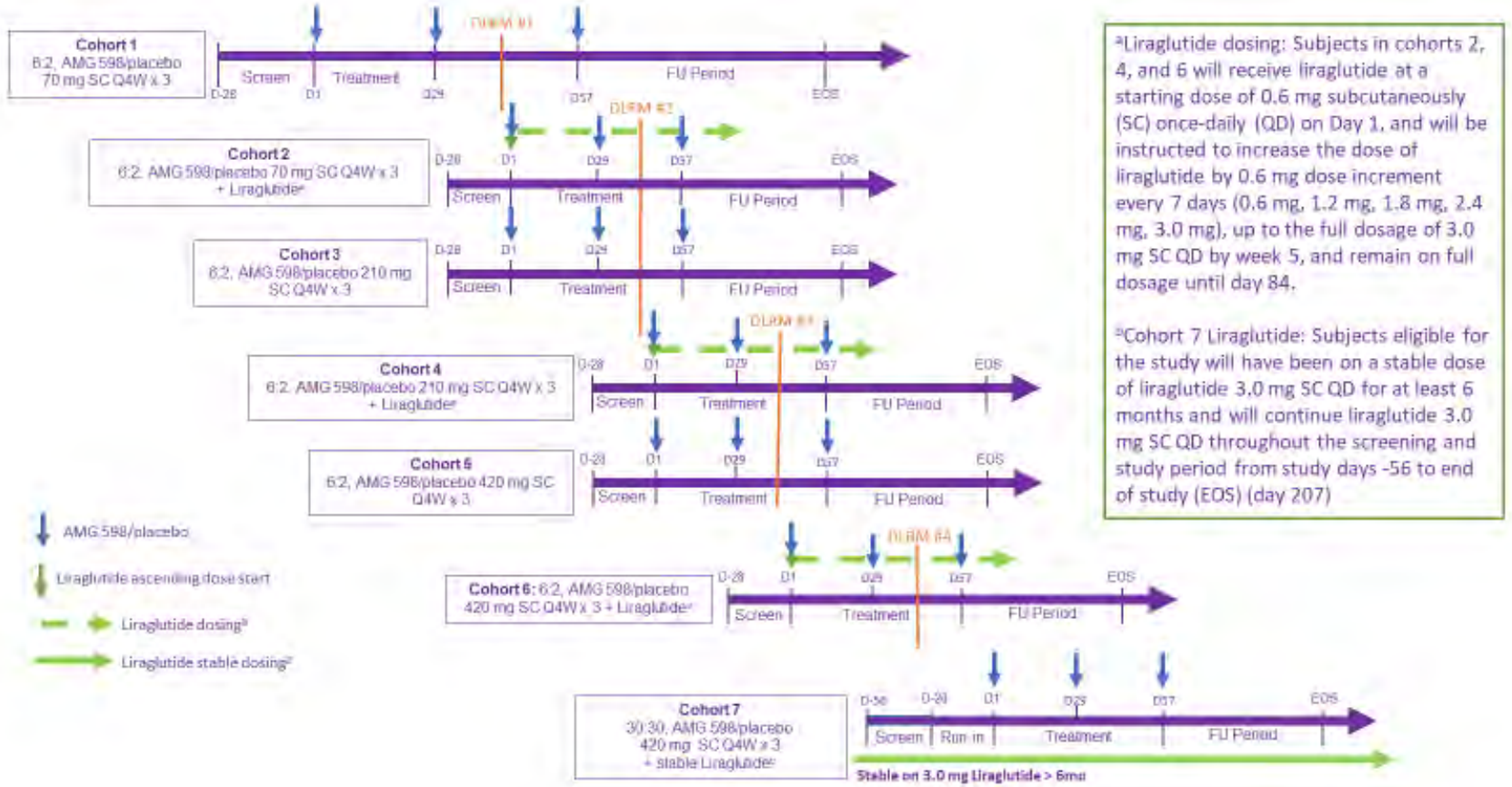
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen, Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



2.2 Schedule of Activities

Table 2-1. Schedule of Activities for Cohorts 1, 3 and 5

	Screening								Treatment																				Follow up						EOS
Study Day	-28 to -3	-2	-1						1	6						8	15	22	29	36	57	62	64							71	85	99	113	127	169	207
Visit Windows										± 1 day										± 1 day			± 1 days							± 2 days	± 3 days			± 7 days		
Time (in minutes)[b]			-15	0	30	60	120	240		-15	0	30	60	120	240								-15	0	30	60	120	240							
Time (in hours)[b]			Pre	0	0.5	1	2	4		Pre	0	0.5	1	2	4								Pre	0	0.5	1	2	4							
General and Laboratory Assessments																																			
In house residency[m]		⟷							⟷	⟷													⟷												
Informed Consent	X																																		
Medical History	X																																		
Demographics	X																																		
Physical Examination[c]	X	X[c]																	X[a]		X[a]									X[c]		X			X[c]
CSSRS + PHQ9	X	X																	X[a]		X[a]									X					X
Body Weight	X	X							X[a]							X	X	X	X[a]	X	X[a]		X							X		X	X	X	X
Height	X																																		
Body Mass Index	X																																		
Waist Circumference									X[a]										X[a]		X[a]									X			X	X	X
Vital Signs (BP, HR, RR, TEMP)	X	X							X[a]	X						X	X	X	X[a]	X	X[a]		X							X		X	X	X	X
12-Lead ECG[d,e]	X	X							X[e]	X						X		X	X[a]	X	X[a]		X							X		X		X	X
Concomitant Medications	⟷																																		
Adverse Event Recording									⟷																										
Serious Adverse Event Recording	⟷																																		
Clinical Chemistry[f,h]	X	X														X			X[a]	X	X[a]		X							X		X		X	X
Clinical Hematology[f,h]	X	X														X			X[a]	X	X[a]		X							X		X		X	X
Coagulation Tests[f]	X																																		
eGFR[f,h]	X	X																																	X
Serum CTX and P1NP[g,h]		X														X			X[a]	X	X[a]		X							X				X	X
Serum Amylase and Lipase[f,h]		X														X			X[a]	X	X[a]		X							X				X	X
Urinalysis[f]	X	X																												X					X

Footnotes defined on last page of the table

Table 2-1. Schedule of Activities for Cohorts 1, 3 and 5

	Screening								Treatment																				Follow up						EOS
Study Day	-28 to -3	-2	-1						1	6						8	15	22	29	36	57	62	64							71	85	99	113	127	169	207
Visit Windows										± 1 day										± 1 day			± 1 days							± 2 days		± 3 days		± 7 days		
Time (in minutes)[b]			-15	0	30	60	120	240		-15	0	30	60	120	240								-15	0	30	60	120	240							
Time (in hours)[b]			Pre	0	0.5	1	2	4		Pre	0	0.5	1	2	4								Pre	0	0.5	1	2	4							
General and Laboratory Assessments																																			
Urinalysis[f]	X	X																												X					X
Alcohol, Continine and Drug Screen[f]	X	X																																	
HIV, HBcAb, HBsAg, and HepCAb[f,h]	X																																		
Pregnancy Test[f,i]	X[i]	X[i]																																	
Serum FSH Test (Females Only)[f]	X[k]																																		
MMTT				X							X													X											
Dosing																																			
Study Drug Administration (SC)									X										X		X														
Blood Samples (± window)			± 2 min							± 2 min													± 2 min												
Serum PK[g]									X[a]	X						X	X	X	X[a]	X	X[a]	X	X							X	X	X	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, GIP, GLP-1 and Glucagon)[g,h]				X	X	X	X	X			X	X	X	X	X				X[a]		X[a]			X	X	X	X	X		X					X
Serum PD (FFA)[g,h]				X	X	X	X	X			X	X	X	X	X				X[a]		X[a]			X	X	X	X	X		X					X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides)[f,j]	X								X[a]										X[a]		X[a]		X							X					X
HbA1c[f,h]	X																													X				X	X
Pharmacogenetic[h]			X													X																			
Biomarker Development[h]			X													X				X			X										X		X
Anti-AMG 598 Antibody									X[a]										X[a]											X				X	X
Imaging																																			
DXA Scan[h]		X																												X				X	

Footnotes defined on next page

ECG = electrocardiogram; DXA= Dual-Energy X-ray absorptiometry; Mixed Meal Tolerance Test (MMTT)
[a] Pre-dose assessments
[b] Time in minutes/hours relative to the start time of standardized meal during MMT test and start of each investigational product dose administration during Treatment and Follow-up periods.
[c] Physical exam to include neurological assessment
[d] Single ECG at screening and triplicate (30 seconds apart) at other timepoints
[e] 3 sets of triplicate ECGs at least 30 min apart (-90, -60, and -30 minutes prior to dosing)
[f] Analyzed at the local laboratory
[g] Analyzed at the central laboratory
[h] 10-hour fasting is required at all timepoints
[i] Serum pregnancy test at screening and EOS
[j] Urine pregnancy test
[k] Serum FSH Test (female only) for postmenopausal status confirmation
[l] Local laboratory at screening, then central lab at other timepoints
[m] In house residency day -2 to 1 (2 nights; second overnight, day -1 to 1, is optional), days 5 to 6 (1 night with +/- 1 day start window), day 62 to 64 (2 nights with +/- 1 day start window; first overnight, day 62 to 63, is optional)
[n] DXA scan may be performed within 3 days prior to day 1 or within ±3 days of day 85 and 169 visits

Table 2-2. Schedule of Activities for Cohorts 2, 4 and 6

Activity	Screening		Treatment											Follow up					EOS
Study Day	-28 to -2	-1	1	6	8	15	22	29	36	57	62	64	71	85	99	113	127	169	207
Visit Windows				± 1 day					± 1 day		± 1 day		± 2 days	± 3 days			± 7 days		
General and Laboratory Assessments																			
In house residency[m]		⟷		⟷							⟷								
Informed Consent	X																		
Medical History	X																		
Demographics	X																		
Physical Examination[c]	X	X[c]						X[a]		X[a]				X[c]		X			X[c]
CSSRS + PHQ9	X	X						X[a]		X[a]				X					X
Body Weight	X	X	X[a]		X	X	X	X[a]	X	X[a]	X	X	X	X		X	X	X	X
Height	X																		
Body Mass Index	X																		
Waist Circumference			X[a]					X[a]		X[a]				X			X	X	X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[a]	X		X	X	X[a]	X	X[a]	X	X	X	X		X	X	X	X
12-Lead ECG[d,e]	X	X	X[e]	X	X		X	X[a]	X	X[a]	X	X		X		X		X	X
Concomitant Medications	⟷																		⟷
Adverse Event Recording			⟷																⟷
Serious Adverse Event Recording	⟷																		⟷
Clinical Chemistry[f,n]	X	X			X			X[a]	X	X[a]	X	X		X		X		X	X
Clinical Hematology[f,n]	X	X			X			X[a]	X	X[a]	X	X		X		X		X	X
Coagulation Tests[f]	X																		
eGFR[f,n]	X	X																	X
Serum CTX and P1NP[g,n]		X			X			X[a]	X	X[a]	X	X		X				X	X
Serum Amylase and Lipase[f,n]		X			X			X[a]	X	X[a]	X	X		X				X	X
Urinalysis[f]	X	X												X					X
Alcohol, Continine and Drug Screen[f]	X	X																	
HIV, HBcAb, HBsAg, and HepCAb[f,n]	X																		
Pregnancy Test[i,j]	X[i]	X[j]																	
Serum FSH Test (Females Only)[k]	X[k]																		
Dosing																			
Study Drug Administration (SC)			X					X		X									
Liraglutide Administration (SC)[o]			X[o]																

Footnotes defined on next page of the table

Table 2-2. Schedule of Activities for Cohorts 2, 4 and 6

Activity	Screening		Treatment											Follow up					EOS
Study Day	-28 to -2	-1	1	6	8	15	22	29	36	57	62	64	71	85	99	113	127	169	207
Visit Windows				± 1 day					± 1 day		± 1 day		± 2 days	± 3 days			± 7 days		
PK and Other Blood Samples																			
Serum PK (AMG 598)[g]			X[a]	X	X	X	X	X[a]	X	X[a]	X	X	X	X	X	X	X	X	X
Plasma PK (liraglutide)[g]			X[a]					X[a]		X[a]				X					X
Plasma PD (Insulin, C-peptide, Glucose, GIP, GLP-1, and Glucagon)[g,h]			X[a]	X				X[a]		X[a]	X	X		X					X
Serum PD (FFA)[g,h]			X[a]	X				X[a]		X[a]	X	X		X					X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides)[i,h]	X		X[a]					X[a]		X[a]	X	X		X					X
HbA1c[i,k]	X													X				X	X
Pharmacogenetic[n]		X			X														
Biomarker Development[n]		X			X				X		X	X					X		X
Anti-AMG 598 Antibody			X[a]					X[a]						X				X	X
Imaging																			
DXA Scan[n]		X												X				X	

ECG = electrocardiogram; DXA= Dual-Energy X-ray absorptiometry

[a] Pre-dose assessments
[b] Liraglutide dose escalation; starting dose 0.6 mg SC QD on Day 1, increase by 0.6 mg dose increment Q1W up to the full dose of 3.0 mg SC QD at week 5. Remain at 3.0 mg SC QD from week 5 until Day 84, inclusive.
[c] Physical exam to include neurological assessment
[d] Single ECG at screening and triplicate (30 seconds apart) at other timepoints
[e] 3 sets of triplicates at least 30 min apart (-90, -60, and -30 minutes prior to dosing)
[f] Analyzed at the local laboratory
[g] Analyzed at the central laboratory
[h] 10-hour fasting is required at all timepoints
[i] Serum pregnancy test at screening and EOS
[j] Urine pregnancy test
[k] Serum FSH Test (female only) for postmenopausal status confirmation
[l] Local laboratory at screening, then central lab at other timepoints
[m] Optional in-house residency day -1 to 1 (1 night), days 6 to 8 (2 nights with +/- 1 day start window), day 62 to 64 (2 nights with +/- 1 day start window)
[n] DXA scan may be performed within 3 days prior to day 1 or within ±3 days of day 85 and 169 visits

Table 2-3. Schedule of Activities for Cohort 7

Activity	Screening	Run-in	Treatment					Follow up		EOS
Study Day	-56 to-29	-28	1	15	29	57	71	85	145	207
Visit Windows		±2 days		±2 days	±1 day	±1 day	±3 days	± 7 days		
General and Laboratory Assessments										
Informed Consent	X									
Medical History	X									
Demographics	X									
Physical Examination	X		X[a,c]		X[a]	X[a]		X[c]		X[c]
CSSRS + PHQ9	X	X	X[a]		X[a]	X[a]		X		X
Body Weight	X	X	X[a]	X	X[a]	X[a]	X	X	X	X
Height	X									
Body Mass Index	X									
Waist Circumference			X[a]		X[a]	X[a]		X	X	X
Vital Signs (BP, HR, RR, TEMP)	X	X	X[a]	X	X[a]	X[a]	X	X	X	X
12-Lead ECG[d]	X	X	X[a]		X[a]	X[a]		X		X
Concomitant Medications	←									→
Adverse Event Recording			←							→
Serious Adverse Event Recording	←									→
Clinical Chemistry[e,f]	X		X[a]		X[a]	X[a]		X	X	X
Clinical Hematology[e,f]	X		X[a]		X[a]	X[a]		X	X	X
Coagulation Tests[e,f]	X									
eGFR[e,f]	X		X[a]							X
Serum CTX and P1NP[e,f]			X[a]	X	X[a]	X[a]	X	X	X	X
Serum Amylase and Lipase[e,f]			X[a]	X	X[a]	X[a]	X	X	X	X
Urinalysis[g]	X									
Alcohol, Continine and Drug Screen[h]	X									
HIV, HBcAb, HBsAg, and HepCAb[e]	X									
Pregnancy Test[g,h]	X[g]		X[h,g]		X[h,g]	X[h,g]		X[h]	X[h]	X[g]
Serum FSH Test (Females Only)[i]	X[i]									
Dosing										
Study Drug Administration (SC)		X[j]	X		X	X				
Liraglutide (SC)[b]					X[b]					
PK and Other Blood Samples										
Serum PK[e]			X[a]	X	X[a]	X[a]	X	X	X	
Plasma PK[e]			X[a]	X	X[a]	X[a]	X	X	X	X
Plasma PD (Insulin, C-peptide, Glucose, GIP, GLP-1, and Glucagon)[e,f]			X[a]	X	X[a]	X[a]	X	X		X
Serum PD (FFA)[e,f]			X[a]	X	X[a]	X[a]	X	X		X
Lipid Panel (total cholesterol, LDL-C, HDL-C and triglycerides)[e,f]	X		X[a]		X[a]	X[a]	X			X
HbA1c[e,f]	X		X[a]					X		
Pharmacogenetic[e]			X[a]							
Biomarker Development[e]			X[a]					X		
Anti-AMG 598 Antibody			X[a]		X[a]			X	X	X
Imaging										
Whole body DXA scan[k]			X[k]					X[k]		

ECG = electrocardiogram; DXA= Dual-Energy X-ray absorptiometry

[a] Pre-dose assessments
[b] Subjects to remain on liraglutide 3mg SC QD throughout duration of the study
[c] Physical exam to include neurological assessment
[d] Single ECG
[e] Analyzed at the central laboratory
[f] 10-hour fasting is required at all timepoints
[g] Serum pregnancy test at screening and EOS for all female subjects
[h] Urine pregnancy test for female subjects of reproductive potential
[i] Serum FSH Test (female only) for postmenopausal status confirmation
[j] All subjects receive placebo injection
[k] Whole body DXA scan may be performed within 3 days prior to day 1 or within ±3 days of day 85 visit

3. Introduction

3.1 Study Rationale

Obesity is a growing global health crisis that is in critical need of safe and effective therapies. Currently approved products provide modest weight loss from baseline with issues of discontinuation due to the side effects of nausea and GI intolerability, as well as lack of continued efficacy. The current study evaluates the safety and tolerability, PK, and PD of multiple ascending doses of AMG 598 alone, and in combination with liraglutide, as a potential weight loss therapy for subjects with obesity. AMG 598, a human monoclonal antibody, binds the glucose dependent insulinotropic polypeptide receptor (GIPR), and blocks the binding of its endogenous ligand (glucose-dependent insulinotropic polypeptide [GIP]) preventing activation of the receptor and downstream pathways. Nonclinical animal studies demonstrated that GIPR antagonism resulted in significant (5-8%) weight loss compared to vehicle control. When combined with commercially available glucagon-like peptide-1 (GLP-1) receptor agonists, AMG 598 lead to a > 20% weight reduction in overweight and obese animals. Thus, in addition to evaluating AMG 598 safety and tolerability, PK and PD alone or in combination with liraglutide (a GLP-1 receptor agonist), the current study also examines the safety and preliminary weight loss efficacy of AMG 598 in a cohort of subjects who have been maintained on a stable dose of liraglutide. The sample size for this specific cohort (30:30 subjects in cohort 7) is based on practical considerations and statistical analysis for the detection of meaningful weight loss. The rationale for dose selection was based on PK and safety analysis of preliminary data collected in the first-in-human (FIH) single ascending dose study of AMG 598 in subjects with obesity. The blinded safety data from the AMG 598 FIH study suggests single doses of AMG 598 have been generally well tolerated up to 560 mg SC, with no serious adverse events (SAE), deaths, or withdrawals related to adverse events reported.

3.2 Background

3.2.1 Disease

Obesity represents a major threat to public health and the accompanying health-care costs pose an enormous financial burden (Terranova et al, 2012; Wang et al, 2011). The prevalence of obesity has more than doubled worldwide over the last decades and currently, 600 million adults are obese, defined as having a body mass index (BMI) of >30 kg/m^2 (World Health Organization [WHO], 2016). Obesity is a major risk factor for type 2 diabetes and cardiovascular disease (CVD) and is associated with increased risk of all-cause and CVD-related mortality (Jensen et al, 2014). Additional comorbidities

include nonalcoholic steatohepatitis (NASH), polycystic ovary syndrome, obstructive sleep apnea, osteoarthritis, gallbladder and skin diseases, and several forms of cancer (Jensen et al, 2014). In addition, persons with obesity frequently encounter psychological and social problems such as low self-esteem, prejudice, and discrimination (Kolotkin et al, 2001).

Achieving clinically significant weight loss (> 5%) through lifestyle changes focuses on reduced energy intake and increased physical activity, and can improve risk factors for CVD, delay or prevent the development of type 2 diabetes, and contribute to better quality of life (Jensen 2014, Look AHEAD Research Group, 2013). Exercise and nutritional counseling can be effective in the short term, but many patients will sustain less than 5% weight loss in the long term (Look AHEAD Research Group, 2014). Currently approved weight loss products belong to the following therapeutic classes: GLP-1R agonists (liraglutide [Saxenda®]), 5-HTR agonists (lorcaserin [Belviq®]), noradrenergic agents (phentermine [Adipex-P®]), lipase inhibitors (orlistat [Xenical®/ Alli®]), in addition to fixed combination products (phentermine + topiramate [Qsymia®], and bupropion + naltrexone [Contrave®]). With the currently approved pharmacotherapy for weight management, a modest incremental average weight loss of 2–9 kg can be achieved over and above lifestyle measures. Across phase 3 studies of currently approved products, a greater proportion of individuals with obesity on active medication (44-75%) achieve a reduction in bodyweight > 5% from baseline over 52 weeks than among those assigned to placebo (23%) (Khera et al, 2016). Side effects of currently approved weight loss products vary depending upon their mechanism and include increased blood pressure, tachycardia, restlessness (stimulants like phentermine), flatulence, and diarrhea (medicines that affect fat absorption, such as orlistat), nausea, vomiting, constipation, dry mouth, and dizziness (molecules that directly interfere with neurotransmitter signaling in the brain, such as lorcaserin, bupropion and naltrexone) (Heymsfield and Wadden, 2017). The majority of persons with obesity are generally dissatisfied with weight loss of less than 10 kg, and as a consequence may discontinue pharmacological treatment to avoid the both the costs and side effects accompanying the potential life-long medication (Dalle Grave et al, 2005). Consequently, new pharmacological agents for the treatment of obesity are needed to improve efficacy and reduce side effects.

3.2.2 Amgen Investigational Product Background: AMG 598

3.2.2.1 Pharmacology

AMG 598 is a fully human monoclonal antagonistic antibody that binds the extracellular domain of human GIPR. AMG 598 blocks the binding of the endogenous ligand, GIP, preventing activation of the receptor and accumulation of cyclic adenosine monophosphate (cAMP). GIP and GLP-1 are gut-derived incretin hormones, known for their ability to augment glucose stimulated insulin secretion, and in the case of GLP-1 also recognized to promote satiety (Baggio et al, 2014). As such, GLP-1 analogs are marketed for treatment of type 2 diabetes (T2D), and for weight management in obesity (liraglutide [Saxenda®]). In addition to ingested carbohydrate, dietary fat is a potent stimulant of GIP secretion in humans (Falko et al, 1975), and meal size is positively correlated with postprandial GIP secretion (Vilsboll et al, 2003). The exposure of rodents to a high-fat diet (HFD) leads to increased GIP secretion from K cells in the proximal small intestine (Suzuki, 2013; Tseng 1994). Similarly, acute high fat-feeding in humans also results in a 42% increase in circulating GIP levels before any noticeable body weight increase (Brons et al, 2009).

GIPR has been reproducibly identified in human genetic association studies of BMI measurements (Berndt et al, 2013; Okada et al, 2012; Wen et al, 2012; Speliotes et al, 2010; Yip et al, 1998;). Of the four SNPs (*rs2287019, rs10423928, rs1800437, rs1167664*) which have been described, only one SNP (*rs1800437*) results in a non-synonymous change at residue 354 (E354Q) with the obesity risk allele (E354) leading to an obesity odds ratio of 1.1. Reciprocally, Q354 is associated with reduced incretin effect (Almind et al, 1998) and delayed GIPR membrane recycling (Mohammad et al, 2014) suggesting that Q354 exhibits lower GIPR activity than that of E354, allowing speculation that higher GIPR activity is obesity promoting. GIP, K-cell and GIPR null mice are all resistant to high fat diet induced obesity (Nasteska et al, 2014; Althage et al, 2008; Miyawaki et al, 2002). Notably these changes in adiposity were not associated with profound changes in appetite. Additionally, GIP vaccination (Fulurija et al, 2008) or neutralization (Boylan et al, 2015) lead to reductions in fat mass accumulation. Administration of a mouse specific GIPR antibody (mAb 2.63.1) alone resulted in significant lower weights than placebo (> 5%) in diet induced obese (DIO) mice, and greater than 20% weight reduction when combined with a GLP-1 agonist in DIO mice. Obese cynomolgus monkeys exhibited an 8% weight loss with AMG 598 alone as compared to placebo, and over 20% weight reduction with AMG 598 and a GLP-1 agonist combined.

The mouse, cynomolgus monkey, and human genetic evidence supports the therapeutic concept of developing a GIPR antagonist either alone or in combination with a GLP-1R agonist for the treatment of obesity.

Refer to the AMG 598 Investigator's Brochure (IB) for additional information related to the pharmacology, physical, chemical, and pharmaceutical properties and formulations of AMG 598.

3.2.2.2 Pharmacokinetics

AMG 598 PK was evaluated in single dose-studies in mice and monkeys over the dose ranges of 1 to 10 mg/kg and 0.1 to 3 mg/kg, respectively. Following a single dose, AMG 598 exposure as assessed by maximum observed concentration (C_{max}) and area under the concentration time curve (AUC) was approximately dose-proportional. AMG 598 was absorbed upon SC administration with absolute bioavailability of 80% and 127% in mice and monkeys, respectively, although the estimate for monkeys was not considered reliable due to sampling limitations. AMG 598 demonstrated a long terminal half-life ($t_{1/2,z}$) ranging from 13.6 to 19.3 days and from 10.3 to 20.1 days in mice and monkeys, respectively.

The toxicokinetics (TK) of AMG 598 was characterized in a Good Laboratory Practice study after weekly subcutaneous (SC) doses of 50, 150, and 700 mg/kg administered for 4 weeks in mice. AMG 598 TK was also characterized in a GLP study after weekly SC doses of 6, 30, and 200 mg/kg administered for 4 weeks in cynomolgus monkeys and in a GLP study after weekly SC doses of 30 and 200 mg/kg administered for 13 weeks in cynomolgus monkeys. Following multiple doses, AMG 598 exposure increased approximately dose proportionally over a dose range from 50 to 700 mg/kg and from 6 to 200 mg/kg in mice and monkeys, respectively. AMG 598 exposures were similar (within 2-fold) between male and female animals in both species.

For summary information on preliminary PK in humans, please refer to Section 5.4

3.2.2.3 Toxicology

In compliance with the International Council for Harmonisation (ICH) S6 (R1) and ICH M3 (R2) guidelines, a comprehensive nonclinical toxicology program was conducted to support the proposed clinical study with AMG 598 (ICH S6 (R1), 2011; ICH M3(R2), 2009). The Good Laboratory Practice studies included 4-week SC repeat-dose toxicology studies conducted in cynomolgus monkeys and in mice (for additional information, refer to Investigator's Brochure), one 13-week SC repeat-dose toxicology study in cynomolgus monkeys and a tissue cross reactivity study in a full

panel of human tissues with biotin conjugated AMG 598. AMG 598 binds with equivalent high affinity to human, cynomolgus monkey, and mouse GIPR; however, in regard to inhibition of GIP signaling through GIPR, AMG 598 demonstrates approximately 50-fold decreased potency for mouse GIPR in comparison to human or cynomolgus monkey GIPR.

In the 13-week study in cynomolgus monkeys, AMG 598 (30 or 200 mg/kg administered weekly by SC injection in the subscapular region), liraglutide (1.8 mg administered daily by SC injection in the thigh), and corresponding placebos were administered to 3 monkeys/sex/group. Combinations administered were placebo/placebo, placebo/Liraglutide, AMG 598 (30 or 200 mg/kg)/placebo, and AMG 598 (30 or 200 mg/kg)/Liraglutide. Liraglutide, AMG 598, and AMG 598/Liraglutide were well tolerated at all doses with no effects on mortality, food consumption, coagulation, urinalysis, biomechanical markers of bone turnover, respiration, electrocardiographic (qualitative and quantitative) or ophthalmic assessments. Administration of both AMG 598 and liraglutide did not affect the pharmacokinetic parameters of either drug. Transient decreases in body weights observed in some animals administered liraglutide or 30 mg/kg AMG 598/Liraglutide is an anticipated pharmacologic effect. AMG 598 and AMG 598/Liraglutide-related hematology changes included minimally decreased red blood cell mass in males only at 200 mg/kg AMG 598 and ≥ 30 mg/kg AMG 598/Liraglutide which was associated with minimally to moderately increased reticulocytes and mildly increased red cell distribution width in males at 200 mg/kg AMG 598.

AMG 598/Liraglutide-related clinical chemistry changes included transient minimal increases in total bilirubin, mild decreases in glucose, and moderately to marked decreases in insulin at doses ≥ 30 mg/kg that recovered by day 92, except for decreased insulin at 30 mg/kg. Liraglutide-related changes included transient minimal to mild increases in total bilirubin and mild decreases in glucose and insulin that recovered by day 92.

AMG 598 is immunogenic in the cynomolgus monkey and 16 of the 24 monkeys administered AMG 598 developed anti-drug antibodies (ADA) by end of study. Clinical signs were limited to one male at 200 mg/kg AMG 598 and consisted of skin lesions which correlated to scab formation and a light microscopic finding of ulceration. The skin lesions were related to cutaneous vasculitis which was considered secondary to AMG 598/ADA immune complex (IC) formation. AMG 598 and

AMG 598/Liraglutide-related light microscopic changes of (peri-) vascular mononuclear and mixed cell infiltrates in various tissues were suggestive of ADA/IC-related pathology (Rojko et al 2014, Mease et al, 2017). Two animals (200 mg/kg AMG 598) with (peri)vascular mononuclear and mixed cell infiltrates in multiple organs (including the skin lesions described above) had changes in clinical chemistry parameters that included minimally decreased albumin and mildly increased globulins on day 92 suggestive of an acute phase response. One of these animals also had mild to moderate increases in aspartate aminotransferase, alkaline phosphatase, gamma glutamyltransferase, and total bilirubin on day 92. Because the induction of antibody formation to a human protein in animals is not predictive of potential immunogenicity in human subjects (ICH S6(R1) 2011; Ponce et al, 2009), the light microscopic changes are not predictive for the development of similar changes in human subjects.

Decreases in absolute and relative thymus weights were observed in females administered liraglutide, AMG 598 at 200 mg/kg, or AMG 598/Liraglutide. Light microscopic changes due to the stress of transient body weight loss and ADA/IC formation were observed in the thymus (atrophy), in the pancreas (decreased secretory content), and in the salivary glands (decreased secretory content) in some females at ≥ 30 mg/kg AMG 598/Liraglutide. The no-observed-adverse-effect level (NOAEL) for AMG 598 was determined to be 200 mg/kg either as a monotherapy or in combination with 1.8 mg liraglutide. The NOAEL of 200 mg/kg AMG 598 when administered with 1.8 mg liraglutide corresponded to a mean C_{max} of 4670 µg/mL and an AUC_{last} of 662000 hr·µg/mL on day 85, with anticipated 62X and 61X AUC and C_{max} exposure multiples, respectively, when compared to the highest proposed monthly clinical dose of 420 mg (Table 5-1). The 1.8 mg dose of liraglutide when administered with 200 mg AMG 598 corresponded to a mean C_{max} of 6.75 µg/mL and an AUC_{last} of 75.0 hr·µg/mL on day 91 which corresponds to an approximately 25X exposure multiple above the average steady state concentration ($AUC_{\tau/24\ hr}$) of 116 ng/mL for a 3.0 mg dose of liraglutide in obese patients (Saxenda® Label).

3.2.2.4 Reproductive and Developmental Toxicity

No nonclinical toxicity studies of the effects of AMG 598 on reproduction and development have been conducted. Females of child-bearing potential may participate in cohort 7 of the study if they are willing to use highly effective method of contraception during treatment and for an additional 5 months after the last dose of AMG 598.
AMG 598 is a monoclonal antibody. The embryo-fetal exposure of monoclonal antibodies during organogenesis is understood to be low in humans based on current

scientific evidence, and therefore the developmental toxicity study with AMG 598 will be conducted later in drug development (ICH M3 R2, 2009). Male subjects with partners of childbearing potential must practice a highly effective method of birth control for the duration of the study and continuing for 5 months after the last dose of investigational product. Refer to Section 12.5 for additional contraceptive information.

3.2.2.5 Clinical Experience

As of August 2018, in the ongoing FIH single ascending dose trial of AMG 598 in subjects with obesity, 56 subjects have received a single dose of AMG 598 or placebo. The blinded safety data through day 15 of the 560 mg SC dose cohort supports the dose range to be evaluated in this study. In addition, a cohort where subjects received a single dose of AMG 598 560 mg SC in combination with liraglutide 0.6 mg SC QD for 7 days has completed dosing. Single ascending doses of AMG 598 have been safe and generally well tolerated. No SAEs or deaths have been reported, and most AEs reported were mild, with one moderate adverse event associated with gastroenteritis.

3.2.3 Non-Amgen Non-investigational Product Background: Liraglutide (Saxenda®)

Liraglutide, a GLP-1 receptor agonist, is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (eg hypertension, type 2 diabetes mellitus, or dyslipidemia).

Cohorts 2, 4, and 6: Subjects will begin receiving liraglutide (0.6 mg SC QD) on day 1, and increased doses of liraglutide (0.6 mg dose increment every 7 days), up to the full dosage of 3.0 mg by week 5, and continue to receive 3.0 mg SC, QD until Day 84, inclusive. If subjects do not tolerate an increased dose during dose escalation, dose escalation may be delayed for approximately one additional week. See Table 3-1.

Table 3-1. Liraglutide (Saxenda®) Dose Escalation Schedule

Week	1	2	3	4	5
Daily Dose (mg)	0.6	1.2	1.8	2.4	3

Cohort 7: Subjects that have been on liraglutide (3.0 mg SC QD) for 6 months will continue to be administered liraglutide (3.0 mg SC QD) for the duration of the study.

Liraglutide is manufactured by Novo Nordisk Inc. and is provided as an injection-ready, pre-filled, multi-dose pen containing 3 mL (6 mg/mL). Doses of liraglutide will be

self-administered with the pre-filled multi-dose pen. Details will be provided in the Investigational Product Instruction Manual (IPIM) and the subject will be trained on the Instructions for Use (IFU). A dosing diary will be used to track self-administered dosing.

Refer to the regional manufacturer package insert for additional information.

3.3 Benefit/Risk Assessment

The potential benefits of AMG 598 alone, or in combination with liraglutide, include the anticipated weight loss, and improved cardiovascular risk factors associated with weight loss. Potential risks of AMG 598, as anticipated from animal data and the literature, are described below in Section 3.3.3.

The following benefit risk assessment supports the conduct of this clinical trial. Please refer to the Investigator's Brochure for further data on AMG 598.

3.3.1 Therapeutic Context

Obesity, with its increasing incidence, associated comorbidities and negative impact on well-being, constitutes a growing crisis and critical unmet need in healthcare. Internal non-clinical studies have established a wealth of evidence that AMG 598 targets a pathway that both genetically and physiologically is associated with weight loss. AMG 598 was well tolerated in the FIH single ascending dose study. The current multi-dose study examines the safety and preliminary efficacy of AMG 598 as a weight loss therapy.

3.3.2 Key Benefits

The key anticipated benefits of AMG 598 include clinically meaningful weight loss and its associated benefits of improved cardiovascular health, glucose metabolism, and overall well-being, as well as potential reduced cancer risk.

3.3.3 Key Risks

Potential risks of AMG 598, as anticipated by evidence from animal data and the literature, include those commonly associated with therapeutic antibody administration including local (eg, injection site) reactions, systemic (eg, hypersensitivity) reactions and immunogenicity (ie, the development of anti-AMG 598 antibodies).

Key potential risks detailed below:

1. Injection or allergic reaction – Injection or allergic reactions are potential human risks with AMG 598 based on clinical experience with other biologic agents. Subjects will be monitored during and after administration of AMG 598 for infusion or allergic reactions, such as fever, chills, shaking, hypotension, wheezing, itching, nausea, and/or rash. Following SC administration, subjects will be monitored for injection site reactions, which may include redness, tenderness/pain, bruising, warmth, swelling, itching, and/or infection.
2. Immunogenicity – As a biologic, AMG 598 poses a potential risk of anti-drug antibodies (ADA). Antidrug antibodies have been observed in GLP studies involving cynomolgus monkeys. However, induction of antibodies against human proteins in animals are not predictive of immunogenicity in humans. Subjects will be monitored for potential effects of ADA that may include antibody mediated AEs, altered drug exposure, or loss of efficacy. Pharmacokinetic and immunogenicity samples from subjects in this Phase 1 study will be sent to central laboratories for storage and ADA analysis will be performed.
3. Impaired Glucose Tolerance - Given the role of the GIP-GIPR axis in the production of insulin in response to food ingestion, there is a theoretical risk that GIPR antagonism with administration of AMG 598 could negatively affect glucose homeostasis, resulting in impaired glucose tolerance due to decreased insulin release following food consumption. Pharmacology studies in diet-induced obese mice with a murine surrogate antibody to GIPR, and pharmacology and toxicology studies in normal weight and obese mice and cynomolgus monkeys with AMG 598, showed no negative impact on glucose homeostasis with GIPR antagonism as measured by either fasting serum glucose and insulin levels or as serum glucose and insulin responses to glucose tolerance tests. The MMTT to be conducted in cohorts 1, 3, and 5 will assess the potential of AMG 598 to decrease insulin and increase blood glucose levels after a standardized carbohydrate load.

Please refer to the Investigator's Brochure for further data on AMG 598.

3.3.3.1 Risks

Other potential risks identified by evidence from animal data, the literature, or the first in human study (FIH) include the following:

1. Increased Bilirubin – Animal studies have demonstrated minimal transient increases in total bilirubin that are considered non-adverse. Subjects will be monitored for changes in bilirubin.
2. Gastrointestinal effects - Reduced food intake is expected with AMG 598 administration due to the mechanism of action of AMG 598 and nonclinical observations in DIO mice and overweight cynomolgus monkeys. While food intake was not directly measured, subjects did report a mild loss of appetite in the FIH study after a single dose of AMG 598. In the current study, subjects who receive AMG 598 in combination with liraglutide may experience more severe or

prolonged gastrointestinal side effects, such as nausea and vomiting, in greater magnitude than the known side effects of liraglutide alone. Blinded safety data of the FIH single ascending dose study reported 12 (21%) of 56 subjects reported one or more AEs in the GI disorder organ class, most of mild severity, with one moderate severity event of gastroenteritis. Clinical signs and symptoms will be monitored during the study.

Based only on review of the literature, the following assessments have been incorporated into this study:

1. Bone turnover assessments

   As nonclinical evidence in the literature indicates that GIPR signaling may play an anabolic role in the maintenance of bone quality and/or bone mineral density (Hansen et al, 2017; Holst et al, 2016; Torekov et al, 2014), a series of animal studies were conducted where no differences in bone turnover markers, bone mass, bone density, or microarchitecture in the bones were observed in animals receiving mouse GIPR antibody (mAb 2.63.1) indicating that in a hormonally-deficient state, GIPR antagonism does not enhance bone loss. In addition, no changes in bone turnover markers were observed in the 13-week toxicology study of AMG 598 in the cynomolgus monkey. However, to monitor for bone loss in the current multiple dose human study, bone turnover serum markers and bone density scans (by DXA) are included as assessments.

2. Neurologic assessments

   There exists a limited data set in the literature that indicates that impairment of GIPR signaling may decrease sensory and motor neuron function (Yu et al, 2016; Okawa et al, 2014; Buhren et al, 2009). While the nonclinical animal studies conducted do not support this evidence, neurological exams are incorporated as part of the safety assessments in the current study. The neurological exam will include peripheral sensory and motor evaluation, and assessment of gait, pain, position, strength and reflexes.

3. Suicidal ideation assessments

   It is unknown whether AMG 598 may be a central nervous system (CNS)-active study treatment or associated with an increased risk of suicidal ideation or behavior. Liraglutide is a CNS-active study treatment. In addition, there have been some reports of suicidal ideation and behavior when liraglutide has been given to some subjects with obesity. To characterize and mitigate risk, eligibility and monitoring criteria including PHQ-9 and CSSR-S are included in the study assessments.

For full description please refer to Table 2-1 to Table 2-3 Schedule of Activities.

Refer to the AMG 598 IB, Section 7 for additional information related to potential side effects.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of multiple SC doses of AMG 598 administered alone or in combination with liraglutide in subjects with obesity	• Subject incidence of treatment-emergent AEs • Safety laboratory data, vital signs, and 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 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
• To assess the effects of AMG 598 on body weight, waist circumference and 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

4.2 Hypotheses

- 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

5. Study Design

5.1 Overall Design

This is a randomized, placebo-controlled, double-blind, multiple ascending dose study in subjects with obesity. The study consists of 7 cohorts with SC administration of AMG 598 or matching placebo with and without liraglutide.

Approximately 108 subjects (8 per cohort for cohorts 1-6, 60 for cohort 7) will be enrolled. This study will be conducted at approximately 30 sites in the US.

For cohorts 1 to 6, eight subjects will be randomized to receive AMG 598 or placebo SC every 4 weeks (Q4W) x 3 in a 3:1 ratio at the proposed dose levels of 70, 210, and 420 mg on days 1, 29, and 57. All subjects in cohorts 1, 3, and 5 will undergo MMTT on day -1, 6 (+/- 1 day), and day 64 (+/- 1 day). Subjects in cohorts 2, 4, 6 and 7 will also receive liraglutide at up to 3.0 mg SC QD per the treatment schedule.

For cohort 7, sixty subjects that have been on a stable dose of liraglutide (3.0 mg SC QD) for at least 6 months will be randomized in a 1:1 ratio to receive AMG 598 or placebo. Subjects will continue to receive liraglutide (3.0 mg SC QD) and receive one dose of placebo on day -28, as part of a 4-week run-in. Subjects will then receive AMG 598 420 mg or placebo SC Q4W on days 1, 29, 57 in addition to stable liraglutide (3.0 mg SC QD).

Escalation to a higher dose cohort (cohorts 1 to 6) 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 study day 36 for at least 6 out of 8 subjects dosed and upon unanimous recommendation at the DLRM. The planned dose escalation schedule may be modified based on treatment-emergent data (eg, safety and/or PK). Subsequent dosing will be guided by tolerability and safety. Dose adjustments for AMG 598, 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.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 108 subjects will be enrolled in the study, with 8 subjects per cohort (cohort 1-6) and 60 subjects in cohort 7.

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

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

5.2.2 Number of Sites

Approximately 1-4 investigative sites in the United States will enroll into cohorts 1-6 and approximately 30 investigative sites in the United States will enroll into cohort 7.

5.3 End of Study

5.3.1 End of Study Definition

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

5.3.2 Study Duration for Subjects

Cohorts 1 to 6

Subject participation will last up to approximately 235 days. This includes a 28-day screening period, a period of up to 2 days prior to investigational product (IP) administration and an on-study period lasting up to 207 days.

Cohort 7

Subject participation will last up to approximately 263 days. This includes a 28-day screening period, a 28-day run-in period, and an on-study period lasting up to 207 days.

5.4 Justification for Investigational Product Dose

The rationale for the dose selection and frequency (Q4W) in the current study is based on PK/PD analysis of animal data, as well as PK data from the ongoing FIH single ascending dose study of AMG 598 (20170138). In the FIH study, all 7 cohorts, totaling 56 subjects, have received a single dose of AMG 598 or placebo (AMG 598 dose ranges from 21 mg to 560 mg). Preliminary review of the PK data in the FIH single ascending dose study demonstrated linear PK and dose proportional C_{max} (AUC data pending), with a half-life of approximately 27 days (through 560 mg SC). The median peak serum concentrations after SC administration were observed in approximately 7 days. The anticipated exposure margins for the highest planned AMG 598 dose in the current study (420 mg SC Q4W) for C_{max} and AUC are 61 and 62, respectively calculated from the C_{max} and AUC at the NOAEL (200 mg/kg) of AMG 598 in combination with liraglutide in the 13-week toxicology study in monkeys (Table 5-1). The blinded safety data from the AMG 598 FIH single ascending dose study through day 15 of the 560 mg SC dose cohort supports the dose range to be evaluated in this study. In addition, a cohort where subjects received a single dose of AMG 598 560 mg SC in combination with liraglutide 0.6 mg SC QD for 7 days has completed dosing. Single ascending doses of AMG 598 have been safe and generally well tolerated. No SAEs or deaths have been reported, and most AEs reported were mild, with one moderate adverse event associated with gastroenteritis.

Based on the available PK and safety data from cohorts 1 to 6 reviewed at the DLRM #4 (Figure 2-1 Study Schema), the dose regimen for cohort 7 will be AMG 598 420 mg or placebo SC Q4W x 3. AMG 598 420 mg or placebo Q4W SC x 2 (safety data evaluated through study day 36) dosed concomitantly with liraglutide escalation was safe and generally well tolerated.

Table 5-1. Estimated Exposure Margins of AMG 598 for Multiple Doses (Q4W)

Estimated Exposure Margins of AMG 598 for Multiple Doses (NOAEL=200 mg/kg)						
	Dose		Predicted $AUC_{0\text{-}28day,last\ dose}$[a]	Predicted $C_{max,\ last\ dose}$[a]	Exposure Margins[b]	
Cohorts	(mg)	Route	(µg·day/mL)	(µg/mL)	AUC[c]	C_{max}[d]
1 and 2	70	SC	298	12.8	370	365
3 and 4	210	SC	893	38.3	124	122
5 and 6	420	SC	1790	76.6	62	61

[a] PK data (up to 280 mg cohort) from AMG 598 FIH study is used for PK prediction
[b] Based on NOAEL of 200 mg/kg AMG 598 as a monotherapy or in combination with liraglutide in cynomolgus monkeys; $AUC_{0\text{-}7day}$ (study days 85 to 92) = 27600 µg·day/mL (662000 hr*µg/mL divided by 24 hr/day) and C_{max} (study day 86) = 4670 µg/mL from 6 animals that were administered both 200 mg/kg AMG 598 SC weekly and 1.8 mg Liraglutide SC daily for 13 weeks.
[c] AUC margin = $[AUC_{0\text{-}7day,last\ dose,}$cyno]×4/[$AUC_{0\text{-}28day,\ last\ dose}$ human]
[d] C_{max} margin = $[C_{max,last\ dose,}$cyno]/[$C_{max,last\ dose}$ human]

5.5 Patient Input on Study Design

No patient input was obtained for the study design.

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

For Cohorts 1-6, eligibility criteria will be evaluated during screening period.

For Cohort 7, eligibility criteria will be evaluated during the screening period. Subjects will not be randomized into a treatment group until after successful completion of the run-in period. Subjects who do not complete the run-in or Part 2 criteria at Day 1 will be removed from study and may be replaced.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 12.3).

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

6.1 Inclusion Criteria: Part 1

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

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures

102 Males and females ≥ 18 to ≤ 65 years of age, at the time of signing the informed consent

103 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in the protocol

104 Except for obesity, otherwise healthy (or for cohort 7, medically stable as described below) as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and ECGs on day -2 (cohorts 1, 3, and 5), or day -1 (cohorts 2, 4, and 6), and at screening (cohorts 1-7)

For cohort 7, chronic stable medical conditions that are not otherwise excluded are permitted if in the opinion of the investigator, and the Amgen Medical Monitor if consulted, do not pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

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

106 Have a stable body weight (less than 5 kg self-reported change during the previous 8 weeks) prior to screening

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

108 Female subjects must be of non-reproductive potential (cohorts1-6)

Postmenopausal as defined as:

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

109 Male subjects must agree to practice an acceptable method of effective birth control while on study through 5 months after receiving study drug. Acceptable methods of effective birth control include sexual abstinence; vasectomy; or a condom with spermicide (males) in combination with barrier methods (diaphragm, cervical cap or cervical sponge), hormonal birth control or IUD (females)

110 Male subjects must be willing to abstain from sperm donation while on study through 5 months after receiving study drug

111 For cohort 7, currently on liraglutide 3.0 mg SC QD with history of taking liraglutide 3.0 mg SC QD continuously for ≥ 6 months and liraglutide being generally well tolerated per the investigator’s discretion (and subjects plan to continue liraglutide 3.0 mg SC QD)

6.2 Exclusion Criteria: Part 1

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

Other Medical Conditions

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

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

203 Hepatic liver enzymes ALT, AST, alkaline phosphatase (ALP), or total bilirubin (TBIL) levels > 1.5 (cohorts 1-6) or > 2 (cohort 7) times the upper limit of normal (ULN) at screening

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

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

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

207 For cohorts 2, 4, 6, and 7, screening calcitonin ≥ 50 ng/L

208 For cohorts 2, 4, 6, and 7 subjects with a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2; a personal history of non-familial medullary thyroid carcinoma; confirmed chronic pancreatitis or idiopathic acute pancreatitis, or gallbladder disease (ie, cholelithiasis or cholecystitis) not treated with cholecystectomy

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

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

211 Previous surgical treatment for obesity (excluding liposuction if performed >1 year before trial entry)

212 History of major depressive disorder

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

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

215 Any lifetime history of a suicidal attempt or of any suicidal behavior

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

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

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

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

220 Subject has systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 90 mm Hg (cohorts 1-6) or ≥ 95 mm Hg (cohort 7) at screening, or on day -2 (cohorts 1, 3, 5) or day -1 (cohorts 2, 4, 6) or on day -28 (cohort 7). For each visit, if the initial blood pressure is elevated, the reading may be repeated once at least 15 minutes later and the lower of the 2 readings may be used.

221 History of myocardial infarction or stroke, or hospitalization for cardiovascular disease in the 6 months prior to screening

Prior/Concomitant Therapy

222 Cohorts 1 to 6: Use of the following agents are excluded unless there is a prior consultation between the Principal Investigator and Amgen Medical Monitor:

- Prescription and nonprescription drugs within 14 days or 5 half-lives, whichever is longer, before the first dose of investigational product, with exception to acetaminophen up to 2 g per day for analgesia, and hormone replacement therapy (eg, estrogen, thyroid)
- All herbal medicines, vitamins, and supplements consumed by the subject within the 30 days prior to receiving the first dose of investigational product. Exceptions must be reviewed and approved by the investigator and Amgen Medical Monitor
- Current or history of treatment with medications that may cause significant weight gain, within 3 months prior to screening, including systemic corticosteroids (except for a short course of treatment, ie, 7−10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (eg, imipramine, amitriptyline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium)
- Current participation (or within the last 3 months) in an organized weight reduction program or currently using or used within 3 months before screening: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phentermine, naltrexone, bupropion, lorcaserin, or metformin (either by prescription or as part of a clinical trial)

Cohort 7: Use of the following agents are excluded unless there is a prior consultation between the Principal Investigator and Amgen Medical Monitor:

- Current or history of treatment with medications that may cause significant weight gain, within 3 months prior to screening, including systemic corticosteroids (except for a short course of treatment, ie, 7−10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (eg, imipramine, amitriptyline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium)
- Currently using or used within 3 months before screening including, but not limited to: pramlintide, sibutramine, orlistat, zonisamide, topiramate, phentermine, naltrexone, bupropion, lorcaserin, or metformin (either by prescription or as part of a clinical trial).
- Current participation in diets that include extreme calorie restriction or other activity or dietary practices that cannot be maintained for the duration of trial.

Prior/Concurrent Clinical Study Experience

223 Prior exposure to AMG 598, or currently receiving treatment in another investigational device or drug study, or less than 30 days, or 5 half-lives (whichever is longer), since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded

Other Exclusions

224 Female subjects who are lactating/breastfeeding or who plan to breastfeed while on study through 5 months after receiving the last dose of investigational product

225 Male subjects with partners who are pregnant or planning to become pregnant while the subject is on study through 5 months after receiving the last dose of investigational product

226 Female subjects of childbearing potential with a positive pregnancy test assessed at screening (cohort 7) and/or day -1 (cohorts 2, 4, 6) or day -2 (cohorts 1, 3, 5) by a serum pregnancy test and/or urine pregnancy test

227 Female subjects (cohort 7) of childbearing potential unwilling to use highly effective method of contraception during treatment and for an additional 5 months after the last dose of AMG598. Refer to Section 12.5 for additional contraceptive information.

228 Subject has known sensitivity to AMG 598 or components thereof or a history of drug or other allergy that is in the opinion of the investigator or medical monitor (if appropriate), contraindicates their participation

229 Subject has known sensitivity to mammalian derived products

230 For cohorts 2, 4, 6 and 7, subject has a known sensitivity to liraglutide or any product components

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

232 Subject has a history or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen Medical Monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

233 Subject is unwilling or unable to limit alcohol consumption throughout the course of the study. Alcohol is prohibited 48 hours prior to day -2 (cohorts 1, 3, and 5) or day -1 (cohorts 2, 4, 6), day -28 (cohort 7) and is limited to no more than to 2 drinks per day for males and 1 drink per day for females for the duration of the study (1 drink being equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits)

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

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

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

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

238 Subject has donated or lost ≥ 500 mL of blood or plasma within 60 days of day -1

6.3 Inclusion Criteria Part 2 (Cohort 7 only)

112 No change in eligibility since screening as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, vital signs and ECGs on day 1

113 Compliant in taking liraglutide 3.0 mg SC QD and liraglutide being generally well tolerated per the investigator's discretion

6.4 Exclusion Criteria Part 2 (Cohort 7 only)

239 A patient health questionnaire (PHQ-9) score of ≥ 10 up to day 1

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

241 Subject has systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 95 mm Hg on day 1. For each visit, if the initial blood pressure is elevated, the reading may be repeated once at least 15 minutes later and the lower of the 2 readings may be used

242 A corrected QT interval (QTc) of > 450 msec in males or > 470 msec in females up to day 1

6.5 Lifestyle Restrictions

6.5.1 Meals and Dietary Restrictions

Subjects will be required to fast overnight for at least 10 hours prior to all blood draws for routine clinical laboratory, lipid profile and PD assessments per Schedule of Activities. After dosing, no water is allowed for 2 hours, after which water is allowed ad libitum.

6.5.1.1 Mixed Meal Tolerance Test (MMTT)

Subject in cohorts 1, 3 and 5 will receive a mixed meal on day -1, day 6 (+/- 1 day), and 64 (+/- 1 day). A mixed meal tolerance test (to be initiated early in the morning) will be performed after an overnight fast for at least 10 hours. The meal will be a standardized meal (ie, 2 bottles or cans of Ensure Plus®) for all subjects and will be provided by the site. Subjects can take up to 10 minutes to consume the 2 bottles or cans of Ensure Plus®. As part of the MMTT, multiple blood samples will be collected per the Schedule of Activities.

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

6.5.2 Caffeine, Alcohol, and Tobacco

Subjects must limit alcohol consumption throughout the course of the study. Alcohol is prohibited 48 hours prior to admission to the research facility on day -2 (cohorts 1, 3 and 5), day -1 (cohorts 2, 4, 6), day -28 (cohort 7). Additionally, for cohorts 2, 4 and 6, alcohol is prohibited 48 hours prior to day 6 +/- 1 day and day 64 +/- 1 day. For all subjects, alcohol consumption is limited to no more than 2 drinks per day for males, 1 drink per day for females, for the duration of the study (1 drink is equivalent to 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of wine or 1.5 ounces of 80 proof distilled spirits).

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

6.5.3 Activity

Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, and aerobics) for 72 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during the 72-hour period prior to blood collection (eg, walking, watching television, reading).

6.6 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 12.3).

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

For cohorts 1-6, a subject is considered enrolled when the investigator decides that the subject has met all (Part 1) eligibility criteria. The investigator is to document this recommendation and date, in the subject's medical record and in/on the enrollment case report form (CRF).

For cohort 7, the subject will be enrolled after meeting Part 1 eligibility criteria at screening. The subject will be randomized into a treatment regimen if they complete all run-in procedures and meet Part 2 eligibility prior to dosing on day 1. Subjects who do

not complete all run-in procedures, do not meet Part 2 criteria, or meet any other study discontinuation criteria, will complete an early termination run-in visit and will be removed from study. Subjects who are terminated prior to receiving AMG 598/placebo may be replaced.

Each subject who enters into the screening period for the study (defined as the time when the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. Subjects enrolled into cohorts 1-6 will be randomized manually. The subject identification number will be assigned via IVRS/IWRS for Cohort 7. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study. Re-screening of subjects is acceptable upon discussion with and approval by the Amgen Medical Monitor.

6.7 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened with approval by the Amgen Medical Monitor. Refer to Section 9.1.1.

7. Treatments

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

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

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] AMG 598	Placebo
Dosage Formulation	Colorless to slightly yellow liquid drug product in a 5 mL glass vial (12 vials per box) filled with a 1 mL deliverable volume of 70 mg/mL. The specific packaging dimensions are 8.9 x 6.7 x 4.5 cm.	Placebo will be presented in identical containers, and stored/packaged the same as AMG 598
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Varies per treatment cohort	
Route of Administration	SC injection	
Accountability	The unblinded pharmacist must provide AMG 598 or placebo from the Amgen supplied stock according to the unblinded randomization log. The concentration of preparation, quantity, dose, start date/time, and lot number of AMG 598 is to be recorded on each subject's CRF(s).	
Dosing Instructions	Administration of AMG 598 or placebo requires specific training which must be completed and documented prior to undertaking any administration related activities. AMG 598 will be delivered as 1+ injections to the abdomen. Dosing instructions are provided in the IPIM.	

SC = subcutaneous
[a] AMG 598 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Non-investigational Products

Liraglutide (Saxenda®) is manufactured by Novo Nordisk Inc. and is provided as an injection-ready, pre-filled, multi-dose pen containing 3 mL (6 mg/mL).

Liraglutide is sourced and provided by the site and is not manufactured, packaged or distributed using Amgen clinical study drug distribution procedures

Cohorts 2, 4, and 6: 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 through Day 84. If subjects do not tolerate an increased dose during dose escalation, dose escalation may be delayed for approximately one additional week.

Cohort 7: Subjects that have been on liraglutide (3 mg SC QD) for 6 months will continue to receive liraglutide (3 mg SC QD) for the duration of the study.

For Cohorts 2, 4, 6 and 7, liraglutide administration should occur 30 – 60 mins after AMG 598 administration on days 1, 29 and 57 when both products are administered. Liraglutide must be to be stored, prepared and dosed according to the package insert and IPIM.

7.1.3 Medical Devices

This section is not applicable for the Amgen investigational product. There are no Amgen medical devices or Amgen combination products in this study.

Other non-investigational medical devices may be used in the conduct of this study, including the liraglutide administration pen, or as part of standard care.

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

7.1.4 Other Protocol-required Therapies

Other than Liraglutide (Saxenda®), there are no other protocol-required therapies.

7.1.5 Other Treatment Procedures

This section is not applicable.

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes drug(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen (ie, investigational product: AMG 598/placebo).

Any product complaint(s) associated with investigational product (AMG 598/placebo) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

Any product complaint(s) associated with non-investigational product (ie, liraglutide) not supplied by Amgen are to be reported to the manufacturer and outcome of any inquiry should be reported to Amgen according to the instructions provided in the IPIM.

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

Cohorts 1-6: With exception to acetaminophen up to 2 g per day for analgesia and hormone replacement therapy (eg, estrogen, thyroid), use of any over-the-counter or prescription medications within the 14 days or 5 half-lives (whichever is longer) prior to dosing on day 1, and for the duration of the study, is not permitted unless to treat a medical emergency. In addition, it is recommended that subjects avoid starting new or changing herbal medicines, vitamins and supplements unless reviewed and approved by the Principal Investigator and Amgen Medical Monitor within 30 days prior to dosing on day 1 and for the duration of the study. Any changes regarding concomitant medications should be recorded on the subject's source documents and the CRF along with the reason for the change.

Cohort 7: Any over-the-counter or prescription medication that is known or suspected to have activity on metabolism or weight will not be allowed during the study, including but not limited to:

- Medications that may cause significant weight gain, including systemic corticosteroids (except for a short course of treatment, ie, 7−10 days), tri-cyclic antidepressants, atypical antipsychotic and mood stabilizers (eg, imipramine, amitriptyline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium).
- Medications that may cause significant weight loss, including, pramlintide, sibutramine, orlistat, zonisamide, topiramate, phentermine, naltrexone, bupropion, lorcaserin, or metformin.
- Diets that include extreme calorie restriction or other activity or dietary practices that cannot be maintained for the duration of trial will not be permitted.

7.2 Method of Treatment Assignment

On day -2 (cohorts 1, 3 and 5) or day -1 (cohorts 2, 4 and 6), or day 1 (cohort 7) eligible subjects will be randomized to a treatment assignment in a double-blind fashion. Within

each cohort, subjects will be randomly assigned in a 3:1 ratio (or 1:1 ratio in cohort 7) to receive either AMG 598 or placebo.

The randomization will be performed manually for cohorts 1-6 and, for cohort 7, by IVRS/IWRS. Subjects will be assigned a randomization number based in sequential order in which they qualified to be randomized. Subjects will be considered randomized once a unique subject randomization number has been assigned. Dosing should occur within 2 days of randomization for cohorts 1, 3 and 5, and 1 day of randomization for cohorts 2, 4, 6 and 7. The randomization date is to be documented in the subject's medical records and on the enrollment case report form (CRF).

A randomization schedule, based on a computer-generated randomization list prepared by Amgen, will be provided to the unblinded pharmacist at the site. The unblinded pharmacist will prepare all treatments accordingly and will randomize all subjects based on the randomization schedule.

7.3 Blinding

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

7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

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

should not be distributed to the investigators or subjects prior to the study being formally unblinded.

7.4 Dose Modification

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

Dose Level Review Meetings (DLRM) will be held to review data, monitor safety and make dose change recommendations. The DLRM members will be composed of the Principal Investigator or designee, the Amgen Medical Monitor, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager or designee, and biostatistics representative or designee. Additional members may be added as needed (eg, clinical pharmacology scientist). The DLRM voting members include the Principal Investigator or designee, Amgen Medical Monitor and Amgen Global Safety Officer or designee.

The DLRM members are responsible for dose modification recommendations, which may include escalation to the next planned dose; escalation to an intermediate dose (a dose lower than the next planned dose); de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort. Study data, including demographics, investigational product administration, medical history, concomitant medications, AEs (including SAEs), ECGs, vital signs, and safety laboratory results will be reviewed. If available, emerging PK and PD data may also be reviewed in a manner that does not unblind individual treatment assignments. The data to be reviewed may not have been source data verified or queried.

Data will be reviewed by DLRM members in a blinded manner (ie, treatment assignment will not be revealed) unless unblinding of all subjects in a given cohort is deemed necessary for the review team to make dosing recommendations. Unblinding of individual subjects can be performed at any time by the investigator or Amgen if deemed necessary for subject safety. If deemed necessary, unblinding will be performed according to Amgen standard procedures.

Escalation to a higher dose or combination 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 study day 36 for at least 6 out of 8 subjects dosed in a given cohort and upon unanimous recommendation at the DLRM. Available data from previous cohorts will also be considered. The next cohort will be open for dosing immediately following the DLRM recommendation.

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 basis, and will be agreed upon by Amgen in coordination with the Principal Investigator.

The review of available safety data and dosing change recommendations will be documented in meeting minutes. Amgen will issue a written notification of the dose change recommendation to investigators.

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

7.4.2.1 Amgen Investigational Product: AMG 598

The reason for dose change of AMG 598 is to be recorded on each subject's CRF(s). Adverse event severity grading scale (12.4 Appendix 4) grading will be used to inform the cohort dose stopping rules as shown in Table 7-2.

For cohorts 1 to 6, dosing will be stopped or modified by the DLRM members if suspected adverse drug reactions and/or changes in safety data (including but not limited to vital signs, ECGs, or clinical laboratory results) are observed and these changes pose a significant health risk. The Amgen Medical Monitor will review data on an ongoing basis, and for cohorts 1 to 6 may suspend dosing and convene a DLRM at any time based on emerging safety data. In addition, for cohorts 1 to 6 dose escalation will be stopped or modified as shown in Table 7-2.

Cohort 7 safety data will be monitored on an ongoing basis by the unblinded medical monitor. In addition, a Safety Surveillance Team (SST) will be convened quarterly at a minimum to review cumulative available study data from cohort 7 to assess risk. An ad-hoc SST may also be convened at any time for reasons such as a significant and unanticipated safety finding. The SST will be comprised of the following study team members, or their delegates: the unblinded Medical Monitor, Clinical Research Study Manager, Global Safety Officer, and Biostatistician. Additional members may be added as needed (eg, clinical pharmacology scientist). Study data, including demographics, investigational product administration, medical history, concomitant medications, AEs (including SAEs), ECGs, vital signs, and safety laboratory results will be reviewed. If available, emerging PK and PD data may also be reviewed. The data to be reviewed may not have been source data verified or queried. Study data will be reviewed by the SST in a blinded manner, unless unblinding is necessary to further evaluate a potential

safety signal. The SST may recommend alteration or termination of enrollment and/or dosing in cohort 7 at any time based on emerging safety information.

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

Table 7-2. Cohort Dose Stopping Rules

Scenario	Action
Any occurrence of a moderate suspected adverse drug reaction in 2 or more subjects in the same cohort	• Stop dosing additional subjects and convene DLRM (if event occurs outside of the regularly scheduled DLRM) • Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance • Consider unblinding as appropriate[1] • Upon unanimous decision by the DLRM members, one of the following decisions may be made: o stop enrollment of the cohort (if applicable) o resume enrollment of the cohort as planned o resume enrollment of the cohort at a lower dose o expand the cohort at the same dose o add a lower dose cohort to the study o escalate to an intermediate dose (a dose lower than the next planned dose) o escalate to the next planned dose
Any occurrence of a severe or greater suspected adverse drug reaction	• Stop dosing additional subjects and convene DLRM (if event occurs outside of the regularly scheduled DLRM) • Review adverse event and all relevant safety data for evidence of relationship to treatment and clinical or medical significance • Consider unblinding as appropriate[1] • If the adverse event is determined by unanimous decision of the DLRM members to be related to study drug (ie, AMG 598, after breaking of the study blind) and clinically or medically significant, no further doses should be administered at this dose and no dose escalation should proceed. Enrollment of the study may continue at a lower dose or a lower dose cohort may be added to the study. • Otherwise (ie, if considered not related to AMG 598 or not clinically relevant), upon unanimous decision of the DLRM members, one of the following decisions may be made: o resume enrollment of the cohort as planned o resume enrollment of the cohort at a lower dose o expand the cohort at the same dose o add a lower dose cohort to the study o escalate to an intermediate dose (a dose lower than the next planned dose) o escalate to the next planned dose

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

7.4.2.2 Non-Amgen Non-investigational Product: Liraglutide (Saxenda®)

The reason for dose change of liraglutide is to be recorded on each subject's CRF(s).

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product AMG 598 and liraglutide during the study are provided in the IPIM.

7.6 Treatment Compliance

Subjects are to follow the guidance provided by the managing physician / investigator.

Noncompliance with the treatment protocol is defined by subjects not taking the complete/correct dose(s), missed doses, failure to meet lifestyle restrictions, failure to adhere to visit schedule as defined in the Schedule of Activities, or any other deviation outlined in the protocol.

As noncompliance may impact subject safety or data integrity, treatment compliance of AMG 598 and/or liraglutide will be monitored via drug accountability records, drug concentration measurements, and medication event monitoring.

Please consult the investigator and Amgen Medical Monitor immediately if a dose has been missed or delayed or if an overdose is suspected.

7.7 Treatment of Overdose

The effects of overdose of AMG 598 are not known. Consult the investigator and Amgen Medical Monitor immediately if an overdose is suspected, or subject experiences signs or symptoms of an adverse event related to a potential overdose.

For liraglutide, refer to the approved product label for advice on overdose and report to Amgen Medical Monitor.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used prior to enrollment will be collected per the timeframes defined in Sections 6.1 and 6.2.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

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

8. Discontinuation Criteria

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 2.2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, as applicable and must document this recommendation in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.3

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Pregnancy
- Protocol-specified criteria (Hepatotoxicity Stopping Rules and Mental Health Criteria Stopping Rules); see Section 7.4 and Section 12.8

8.2 Discontinuation From the Study

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

Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 12.6 for further details).

8.2.1 Reasons for Removal From Run In

Reasons for removal of a subject from the run-in period are:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation

- Non-compliance
- Adverse event
- Subject request
- Pregnancy
- Protocol-specified criteria (Part 2 inclusion/exclusion criteria); see Section 6.3 and 6.4

Subjects removed from run-in will be removed from study.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by Sponsor
- Withdrawal of consent from study
- Death
- Lost to Follow up
- Protocol-specified criteria (Part 2 inclusion/exclusion criteria); see Section 6.3 and 6.4

8.3 Lost to Follow-up

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

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

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

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1 to Table 2-3).

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

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

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any study specific screening procedure or discontinuation of standard therapy for any disallowed therapy. For subjects consenting to participate in cohorts 1-6, after the subject has signed the informed consent form, they will be assigned a subject ID. For subjects consenting to participate in Cohort 7, after the subject has signed the informed consent form, the site will register the subject in the IVRS/IWRS and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days prior to first dose of AMG 598/placebo or, for cohort 7, the placebo at the start of the run-in.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 6.6) as applicable.

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

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

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

9.1.2 Treatment Period and Follow up

Visits will occur per the Schedule of Activities (Section 2.2). On-study visits may be completed within 207 days of day 1. The date of the first dose of protocol-required therapies is defined as day 1 for cohorts 1-6, and the first dose of AMG 598/placebo after randomization for cohort 7. All subsequent doses and study visits will be scheduled based on the day 1 date. The final investigational product dose occurs on day 57.

For Cohorts 2, 4, and 6, liraglutide dosing begins on day 1 and continues through day 84. For Cohort 7, subjects will remain on 3 mg liraglutide SC QD for the duration of the study (6 months prior to screening through EOS).

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+3) days after the end of the last dosing interval of AMG 598/placebo. End of Study visit procedures should be performed at the safety follow-up visit.

9.1.3 End of Study

End of Study (EOS) visit procedures will be performed per the Schedule of Activities (Section 2.2). For subject completing the study, this visit occurs on day 207. If feasible, all EOS procedures should be performed at the final visit for subjects who are removed from study prior to day 207.

9.2 Description of General Study Assessments and Procedures

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

9.2.1 General Assessments

9.2.1.1 Informed Consent

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

9.2.1.2 Demographics

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

9.2.1.3 Medical History

A complete medical history will be obtained at screening by the investigator or designated site physician. Medical history will include information on the subject's current health, psychiatric, and surgical history. Relevant medical history findings will be recorded in the subject's source notes and on the appropriate pages of the CRF. Any unresolved medical history will be graded according to Clinical Adverse Event Severity Grading Scale and is described in Section 12.4.

9.2.1.4 Physical Examination

Physical examination, including periodic neurologic examinations, will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event). The neurological exam will include peripheral sensory and motor evaluation, and assessment of gait, pain, position, strength and reflexes.

9.2.1.5 Physical Measurements

Height [in centimeters] should be measured without shoes. Subjects should be in a clinic gown and without shoes each time body weight [in kilograms] is measured. Body Mass Index should be calculated using the following formula:
BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2.

Waist circumference will also be measured (cm) per the Schedule of Activities. Subjects should be standing and relaxed, with restrictive clothing removed from the abdomen. Waist circumference measurements should be taken directly on the skin with a tension-sensitive, non-elastic tape. The tape should be placed in a horizontal line around the abdomen at the level of the iliac crest. The measurement should be read at the end of a normal respiratory expiration.

9.2.1.6 Substance Abuse History

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

9.2.2 Efficacy Assessments

This section is not applicable.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Section 2.2).

9.2.3.1 Adverse Events

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

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Clinical Adverse Event Severity Grading Scale and is described in Section 12.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of AMG 598/placebo through the end of study are reported using the Event CRF.

9.2.3.1.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after the informed consent through end of study are reported using the Event CRF. All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

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

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 12.4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

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

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Section 12.4.

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

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

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

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

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

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

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

Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

9.2.3.2 Pregnancy and Lactation

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

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 12.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

Further details regarding pregnancy and lactation are provided in Section 12.5

9.2.3.3 Vital Signs

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

9.2.3.4 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. ECGs should be performed in a standardized method, in triplicate, and run consecutively (ie, < 30 seconds apart), prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

- Single ECG at Screening (cohorts 1-6) and at all time points for cohort 7 only
- ≥ 3 baseline ECGs collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (ie, < 30 seconds apart) [ie, total ≥ 9 ECGs] (cohorts 1-6)
- Triplicate ECGs at time points after dosing (cohorts 1-6)

Baseline is defined as day 1 pre-dose for all cohorts. The PI or designated site physician will review all ECGs. ECGs will be transferred electronically to an ECG central reader for analysis per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements.

9.2.3.5 Vital Status

This section is not applicable.

9.2.3.6 Suicidal Risk Monitoring

Liraglutide is considered to be a central nervous system (CNS)-active study treatment. In addition, there have been some reports of suicidal ideation and behavior when it has been given to some subjects with obesity. The sponsor considers it important to monitor for such events before and during this clinical study.

It is unknown whether AMG 598 may be associated with an increased risk of suicidal ideation or behavior.

Subjects being treated with AMG 598 and/or liraglutide must be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration is to be given to discontinuing AMG 598 and/or liraglutide in subjects who experience signs of suicidal ideation or behavior.

Families and caregivers of subjects being treated with AMG 598 and/or liraglutide are to be instructed to monitor subjects for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using C-SSRS and Patient Health Questionnaire 9 (PHQ-9). Refer to Section 12.9 and 12.10 for more information.

9.2.4 Clinical Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 2.2) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal

laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (see Section 2.2).

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

9.2.4.1 Pregnancy Testing

A high sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see (Figure 12-2). Refer to Section 12.5 for contraceptive requirements. Additional pregnancy testing should be performed at monthly intervals during treatment with protocol-required therapies and 30 days +/- 3days after discontinuing protocol-required therapies.

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

9.2.5 Biomarker Assessments

Longitudinal effects on lipid levels (eg, total cholesterol, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], and triglycerides) and potential effects on glycemic control (HbA1c) and bone metabolism (CTX and P1NP) will be assessed as detailed in the Schedule of Activities.

9.2.6 Pharmacokinetic Assessments

All subjects enrolled into the study will have pharmacokinetic samples assessed. Whole blood samples of approximately 5 mL will be collected for each measurement of serum concentrations of AMG 598 and plasma concentration of liraglutide as specified in the Schedule of Activities (Section 2.2). Instructions for the collection and handling of

biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

9.2.7 Pharmacodynamic Assessments

Venous blood samples of approximately 5 to 7.5 mL will be collected for measurement of AMG 598 treatment PD effects at each time point specified in the Schedule of Activities. Concentration-time profiles and AUCs for metabolic parameters (glucose, insulin, c-peptide, GIP, GLP-1, glucagon, and FFAs) will be assessed.

9.2.8 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of obesity and/or to identify subjects who may have positive or negative response to AMG 598. Additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted from residual cell pellets retained from the first plasma PD blood draws.

The final disposition of samples will be described in Section 12.6.

9.2.9 Antibody Testing Procedures

Blood samples for antibody testing are to be collected as outlined in the Schedule of Activities (Section 2.2). Bioanalytical testing for anti-AMG 598 antibodies will be conducted on these samples. Subjects who test positive at the final scheduled study visit, defined as the end of study (EOS) visit, and have clinical sequelae that are considered potentially related to an anti-AMG 598 antibody response will be asked to return for additional follow-up testing. Sample collection and testing will occur approximately every 3 months from EOS until: (1) the antibody response is negative or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of AMG 598. All follow up results, both positive and negative will be communicated to the sites. More frequent testing or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing will not be required where it is established that the subject did not receive AMG 598.

9.2.10 Biomarker Development

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

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

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 598, to investigate the mechanism of action of AMG 598 and/ or further the biological understanding of obesity and related metabolic disorders.

Blood samples (approximately 11 mL per collection) are to be collected for biomarker development at the time points specified in the Schedule of Activities (Section 2.2).

9.2.11 Health Economics

Medical resource utilization and health economics data, associated with medical encounters, may be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards)
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

9.2.12 Optional Substudies

The pharmacogenetic testing is optional in this study.

Obtain confirmation that the pharmacogenetic and future testing portions of the Informed Consent Form has been signed prior to performing optional substudy procedures.

9.2.13 Other Assessments

Dual-energy x-ray absorptiometry (DXA) scans will be conducted as outlined in the Schedule of Activities (Section 2.2). DXA scans for bone density measurements of the

spine and hip/femur will be performed in cohorts 1-6. DXA scans of body composition measurements will be performed in cohort 7.

10. Statistical Considerations

10.1 Sample Size Determination

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.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

10.2.1.1 Safety Analysis Set

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

10.2.1.2 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.

10.2.1.3 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.

10.2.2 Covariates

Baseline values may be used as a covariate in analyses.

10.2.3 Subgroups

No subgroup analyses are planned.

10.2.4 Handling of Missing and Incomplete Data

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

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Interim Analysis and Early Stopping Guidelines

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

10.3.1.2 Primary Analysis

The primary analysis will occur after all subjects in cohorts 1-6 have completed the study.

10.3.1.3 Final Analysis

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

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

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

Data for subjects receiving placebo 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 AMG598 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.

10.3.2.2 Efficacy Analyses

This section is not applicable.

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Primary Safety Endpoint(s)

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

10.3.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term according to the medical dictionary for regulatory activities (MedDRA) terminology. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP or other protocol-required therapies, and treatment emergent adverse events will also be provided. The number and percentage of subjects reporting adverse events will be evaluated for each dose cohort, across dose cohorts, and will also be tabulated by relationship to study drug. Adverse events resulting in treatment discontinuation will be identified.

10.3.2.3.3 Laboratory Test Results

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

10.3.2.3.4 Vital Signs

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

10.3.2.3.5 Physical Measurements

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

10.3.2.3.6 Electrocardiogram

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

10.3.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 598 antibodies at any time will be tabulated by treatment group.

10.3.2.3.8 Exposure to Investigational Product

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

10.3.2.3.9 Exposure to Other Protocol-required Therapy

Descriptive statistics of the number of doses of liraglutide received by each subject will be produced to describe the exposure to liraglutide in Cohorts 2, 4, 6 and 7 (eg, from baseline to end of study).

10.3.2.3.10 Exposure to Concomitant Medication

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

10.3.2.4 Other Analyses

10.3.2.4.1 Secondary Endpoint – Pharmacokinetics Analysis

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 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.

10.3.2.4.2 Exploratory Endpoints

The statistical analyses in this section are considered exploratory in nature and will be performed only when deemed appropriate. The safety analysis set will be used for all exploratory endpoint analysis performed.

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
CFR	U.S. Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
COA	clinical outcomes assessment
CRF	case report form
CRO	contract research organization
CSSR-S	Columbia Suicide Severity Rating Scale
DES	Amgen data element standard
DILI	drug induced liver injury
DLRT	dose level review team
DMC	data monitoring committee
DRT	data review team
ECG	electrocardiogram
Echo	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
Enrollment	Subject randomized to treatment group
Exposure-Response Analysis	mechanism-based modeling & simulation and statistical analyses based on individual pharmacokinetic (PK) exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic (PD) effects, efficacy and safety endpoints.
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GOG PS	Gynecological Oncology Group (GOG) Performance Status

Abbreviation or Term	Definition/Explanation
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormone replacement therapy
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFU	Instructions for Use
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information
KPS	Karnofsky Performance Status
Lansky PFS	Lansky Play-Performance Scale
LVEF	left ventricular ejection fraction
MUGA scan	multigated acquisition scan
NCT	National Clinical Trials
PHQ-9	Patient Health Questionnaire 9
SAT	safety assessment team
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-required therapies are administered to the subject
TBL	total bilirubin
SUSAR	suspected unexpected serious adverse reaction
TMF	trial master file
ULN	upper limit of normal

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory and/or by the local laboratory as described in the Schedule of Activities.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.4 of the protocol.

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

Table 12-1. Analyte Listing

Local Laboratory: Chemistry	Local Laboratory:	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Central Laboratory: Other
Sodium	<u>Drug Screen</u>	Specific gravity	RBC	<u>PD assessments</u>
Potassium	Benzodiazepines	pH	Hemoglobin	Insulin
Chloride	Barbiturates	Blood	Hematocrit	Glucose
Bicarbonate/CO2	Opiates	Protein Glucose	MCV	c-peptide
Total protein	Tetrahydrocannabinol	Bilirubin	MCH	free fatty acids
Albumin	Cocaine	WBC	MCHC	GIP
Calcium	Amphetamines	RBC	Platelets	GLP-1
Glucose	Ethanol (may be performed by a breath test)	Epithelial cells	WBC	Glucagon
BUN or Urea		Bacteria	Differential	HbA1c (local at screening)
Creatinine		Casts	• Total Neutrophils - or- seg. Neutrophils and Bands/Stabs	
Total bilirubin		Crystals		<u>Safety assessments</u>
Direct bilirubin			• Eosinophils	P1NP
ALP	<u>Viral Panel</u>		• Basophils	CTX-1
AST (SGOT)	Hep B surface antigen		• Lymphocytes	
ALT (SGPT)	HBcAb		• Monocytes	<u>Lipid Panel</u>
TSH – screening only	HepCAb			Cholesterol (total)
Calcitonin – screening only	HCV RNA PCR(as necessary)		<u>Coagulation</u>	LDL-C
Tryptase (in the event of a suspected anaphylactic reaction)	HIV[a]		PT/INR	HDL-C
			PTT/APTT	Triglycerides
Amylase	<u>Reproductive</u>			
Lipase	Serum or Urine Pregnancy			
	FSH			

[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

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

12.3 Appendix 3. Study Governance Considerations

Safety Monitoring Committee

A safety monitoring committee was not established for this study.

Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

Informed Consent Process

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

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

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

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

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

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the

informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

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

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

Subjects who are rescreened are required to sign a new informed consent form.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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

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

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

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

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

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

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

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

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All

persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

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

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

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

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

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

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

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

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

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

Amgen (or designee) will perform Self-Evident Corrections to obvious data errors in the clinical trial database. Self-Evident Corrections will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

Source Documents

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

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS)

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

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

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

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Investigational Product Accountability Record(s) and Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable (eg, for liraglutide and administration pen).

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

Study and Site Closure

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine

whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

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

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

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements, change in mental health questionnaire scores), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event serious adverse event information in the Event case report form (CRF).
- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to Investigational product: (AMG 598/placebo), and/or non-Amgen non-investigational other protocol-required therapy (liraglutide) and/or any study-mandated activity/procedure
  - Action taken.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event CRF page.
- If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Amgen Standard Grading Scale as show below:

Grade	Definition
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE[a]	Incapacitating with inability to work or do usual activity

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

Assessment of Causality

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

Follow-up of Adverse Event and Serious Adverse Event

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

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper CRF
• Facsimile transmission of the Serious Adverse Event Report Form (see Figure 12-1 is the preferred method to transmit this information. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.

Figure 12-1. Sample Serious Adverse Event Report Form

AMGEN
20170139
AMG 598

Clinical Trial Serious Adverse Event Report – Phase 1–4
Notify Amgen Within 24 Hours of Knowledge of Incident

☐New
☐Follow-up

AMGEN US SAFETY FAX# : +888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number ( )	Fax Number ( )

2. SUBJECT INFORMATION

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

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____Month____Year_____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.	Date Started Day Month Year	Date Ended Day Month Year	Check only if event re-current before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP or an Amgen device used to administer the IP? If yes see section 10 AMG 598 No Yes	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure, eg, biopsy

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ☐No ☐Yes. If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial # Lot # _____ ☐ Unblind Serial # _____ ☐ Unblind
AMG 598 ***Blinded***							

Figure 12-1. Sample Serious Adverse Event Report Form

AMGEN
20170139
AMG 598

Clinical Trial Serious Adverse Event Report – Phase 1–4
Notify Amgen Within 24 Hours of Knowledge of the event

☐New
☐Follow-up

	Site Number	Subject ID Number	

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

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

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

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

Date Day Month Year	Test / Unit											

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

Date Day Month Year	Additional Tests	Results	Units

Figure 12-1. Sample Serious Adverse Event Report Form

AMGEN 20170139 AMG 598	Clinical Trial Serious Adverse Event Report – Phase 1–4 Verify Amgen Within 24 hours of knowledge of the event	☐New ☐Follow-up

	Site Number	Subject ID Number	

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

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

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

Study-specific contraception requirements for males and females of childbearing potential are outlined below.

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

Definition of Females of Childbearing Potential

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

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

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

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of <1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

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

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

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

Unacceptable Methods of Birth Control for Male and Female Subjects

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

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

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 5 months after last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 5 months after last dose of the investigational product. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 12.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will no longer be eligible to continue in the study and study treatment will be discontinued (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 5 months after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 5 months after last dose of investigational product.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 223.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 5 months after last dose of investigational product after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20170139

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm ▾ / dd ▾ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ▾ /dd ▾ /yyyy ____

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

If yes, provide product (or study drug) stop date: mm ▾ /dd ▾ /yyyy ____

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

5. Pregnancy Information

Pregnant female's LMP mm ▾ / dd ▾ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ▾ / dd ▾ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ▾ / dd ▾ / yyyy ____

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

If yes, provide date of delivery: mm ▾ / dd ▾ / yyyy ____

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20170139

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

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

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

12.6 Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (Table 2-1 to Table 2-3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand obesity and related metabolic disorders, the dose response and/or prediction of response to AMG 598, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments

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

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

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

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

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

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

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

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

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

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, Principal Investigator, and Amgen.

If signs or symptoms recur with rechallenge, then the study drug should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

12.7.1 Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

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

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 12.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

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

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

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

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms

- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

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

Subjects with an increase in score on either the PHQ-9 and/or CSSR-S assessments may meet the criteria for permanent discontinuation of Amgen investigational product or other protocol-required therapies.

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

The following stopping rules apply to subjects for whom an increase in their PHQ-9 and/or CSSR-S sores have been identified.

Table 12-3. Conditions for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Changes in Mental Health Scores

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

PHQ-9 = Patient Health Questionnaire 9 ; CSSR-S = Columbia Suicide Severity Rating Scale

Reporting

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

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

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld permanently due to potential mental health changes as specified in Table 12-3 are to undergo a period of “close observation” until the subject’s care can be transferred to an appropriate mental health professional.

12.9 Appendix 9. Columbia Suicide Severity Rating Scale

Baseline Form (shown below) at screening visit and Since Last Visit Form at all subsequent visits.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Lifetime: Time He/She Felt Most Suicidal

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

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

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

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

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

INTENSITY OF IDEATION

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

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

Most Severe

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

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

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

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

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

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

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

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

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

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

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

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

Amendment 3

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 Subjects With Obesity

Amgen Protocol Number: AMG 598 20170139

Amendment Date: 25 June 2019

Rationale:

The following updates were made to the protocol, dated 15 February 2019:

- The dose regimen for Cohort 7 was added following the review of available safety and PK data from cohorts 1 through 6
- Inclusion and exclusion criteria were modified for cohort 7 to allow chronic stable medical conditions, including updates to laboratory reference ranges, and allowed concomitant medications
- A Safety Surveillance Team (SST) was added for ongoing safety review of Cohort 7 emergent data
- Criteria for rechallenge of Amgen investigational product after potential hepatotoxicity were added
- Visit windows were added to the cohort 7 Schedule of Assessments
- Bone mineral density (BMD) measurement clarified to state specifically in spine and hip/femur in cohort 1-6 DXA description
- Mental health questionnaire appendices updated to include the specific forms to be used at the sites

Amendment 2

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 Subjects With Obesity

Amgen Protocol Number: AMG 598 20170139

Amendment Date: 15 Feb 2019

Rationale:

The following updates were made to the protocol, dated 07 November 2018:

- Cohort 7 visits and procedures were streamlined to reduce complexity and burden on subjects completing the study.
- Primary analysis of data from escalation cohorts 1-6 was added in additional to final analysis of all subjects in cohorts 1-7.
- Objective and endpoint language was updated to clarify that potential biomarkers, including but not limited to inflammatory and adipose tissue markers, are one of the PD effects of AMG 598 that will be evaluated in this study.
- Protocol language was updated to reflect that spine and femur bone mineral density will be evaluated by dual energy x-ray absorptiometry (DXA) in subjects in cohorts 1-6, while total body composition, including bone mineral content, will be evaluated by DXA in subjects in cohort 7.
- DXA visit windows added.
- Typographical and formatting errors throughout the protocol were fixed.

Amendment 1

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 Subjects With Obesity

Amgen Protocol Number: AMG 598 20170139

Amendment Date: 07 November 2018

Rationale:

In response to an FDA request, analysis of AMG 598 anti-drug antibody (ADA) samples will be conducted. In addition, the exclusion criteria were updated to exclude previous exposure to AMG 598.

Typographical errors and inconsistencies throughout the protocol were fixed.