2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 145

Name of Active Ingredient: AMG 145 (fully human monoclonal immunoglobulin G2 [IgG2] directed against proprotein convertase subtilisin/kexin type 9 [PCSK9])

Title of Study: A Randomized, Placebo- and Ezetimibe-controlled, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Hypercholesterolemic Subjects With a 10-year Framingham Risk Score of 10% or Less (MENDEL: **M**onoclonal antibody against PCSK9 to reduce **E**levated LDL-C in subjects currently **N**ot receiving **D**rug therapy for **E**asing **L**ipid levels)

Investigators and Study Centers: This study was conducted at 52 centers in the United States, Canada, Australia, Belgium, and Denmark. A listing of participating investigators and their associated study centers is included in Appendix 4.

Publications: None at the time this report was written.

Study Period: 06 July 2011 (date first subject enrolled) to 02 March 2012 (date last subject completed study)

Development Phase: 2

Objectives:

AMG 145 is a fully human monoclonal IgG2 that is being developed for the treatment of hyperlipidemia. AMG 145 binds to PCSK9 and prevents the binding of PCSK9 with the hepatic low density lipoprotein receptor (LDLR). Because PCSK9 down regulates LDLR on the hepatic cell surface, the inhibition of PCSK9 by AMG 145 leads to increased LDLR expression and subsequent decreased circulating concentrations of low density lipoprotein cholesterol (LDL-C).

The present study was designed to investigate the safety and efficacy of AMG 145 delivered as monotherapy in subjects with hypercholesterolemia.

The primary objective of the study was to evaluate the effect of 12 weeks of subcutaneous (SC) AMG 145 administered once every 2 weeks (Q2W) or once every 4 weeks (Q4W), compared with placebo, on the percent change from baseline in LDL-C when used as monotherapy in subjects with hypercholesterolemia.

The secondary objectives were:

- to evaluate the safety and tolerability of 6 dose regimens of SC AMG 145 monotherapy, compared with placebo and with ezetimibe, in subjects with hypercholesterolemia.
- to assess the effects of 12 weeks of SC AMG 145 monotherapy, ezetimibe, and placebo on absolute change in LDL-C, and percent change in non-high density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/high density lipoprotein cholesterol (HDL-C) ratio, and ApoB/apolipoprotein A-1 (ApoA1) ratio in subjects with hypercholesterolemia.
- to characterize the pharmacokinetics (PK) of AMG 145 after SC injection in subjects with hypercholesterolemia

Exploratory objectives are provided in Section 6.3.

Methodology: This randomized, placebo- and ezetimibe-controlled, dose-ranging phase 2 study was designed to evaluate the efficacy and safety of 12 weeks of SC AMG 145 compared with placebo when administered as monotherapy Q2W or Q4W on percent change from baseline in LDL-C in subjects with hypercholesterolemia. In order to allow a placebo controlled design, subjects with a 10-year Framingham risk score of 10% or less were enrolled. After a 6-week screening and placebo run-in period, eligible subjects were randomized with equal allocation into 1 of 9 treatment groups as shown below. Randomization was stratified on the basis of screening LDL-C concentration (< 130 mg/dL [3.4 mmol/L] or ≥ 130 mg/dL).

Treatment Group	IP and Dose	Frequency	Planned N
1	AMG 145, 70 mg	Q2W x 6	45
2	AMG 145, 105 mg	Q2W x 6	45
3	AMG 145, 140 mg	Q2W x 6	45
4	Placebo	Q2W x 6	45
5	AMG 145, 280 mg	Q4W x 3	45
6	AMG 145, 350 mg	Q4W x 3	45
7	AMG 145, 420 mg	Q4W x 3	45
8	Placebo	Q4W x 3	45
9	Ezetimibe, 10 mg	once daily, 12 weeks	45

IP = investigational product; Q2W = once every 2 weeks; Q4W = once every 4 weeks

On the day of randomization (day 1), subjects received their first dose of investigational product (IP) and returned to the study center at weeks 2, 4, 6, 8, 10, 12, and 14 (Q2W group only at this visit) for collection of study assessments, including samples for the determination of lipid parameters. The end-of-study (EOS) visit occurred at week 12 for subjects randomized to ezetimibe and the Q4W IP schedule and at week 14 for those subjects randomized to the Q2W IP schedule.

Concentrations of AMG 145 and PCSK9 were measured in all subjects at scheduled visits during the study. Additionally, all subjects were invited to participate in an optional PK substudy that required 2 additional study center visits at weeks 9 and 11.

Number of Subjects Planned: 405 (45 subjects per treatment group)

Number of Subjects Enrolled: 411 subjects were randomized

Diagnosis and Main Criteria for Eligibility:

Eligible subjects were adult men and women 18 to 75 years of age, inclusive, with fasting LDL-C ≥ 100 mg/dL and < 190 mg/dL and a fasting triglyceride ≤ 400 mg/dL. In order to allow the placebo controlled design, subjects were required to have a National Cholesterol Education Program Adult Treatment Panel III Framingham risk score of 10% or less.

Subjects were excluded from participation if they had used a lipid-regulating drug in the last 3 months prior to LDL-C screening. Subjects were also excluded if they had a history or evidence of clinically significant diseases and conditions that would pose a risk to their safety or interfere with the study evaluation, procedures, or completion.

A complete list of subject inclusion and exclusion criteria is provided in Section 4 of the protocol (Appendix 1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:
AMG 145 was provided as a sterile, clear, colorless, frozen liquid at a concentration of 70 mg/mL formulated with [redacted] AMG 145 was administered SC to assigned groups at doses of 70, 105, and 140 mg Q2W or 280, 350, and 420 mg Q4W in volumes of 2 mL (Q2W dosing) or 6 mL (Q4W dosing) as described below to achieve the assigned dosing concentration. Doses could be split into several injections. In order to maintain blinding among the treatment groups, AMG 145 and placebo were administered as follows:

Treatment Group	Total AMG 145 (70 mg/mL) Volume (volume extracted per vial[a], mL)	Total Placebo Volume (volume extracted per vial, mL)
Placebo Q2W	None	2 mL (0.5 + 0.5 + 0.5 + 0.5)
AMG 145 70 mg Q2W	1 mL (0.5 + 0.5)	1 mL (0.5 + 0.5)
AMG 145 105 mg Q2W	1.5 mL (0.5 + 0.5 + 0.5)	0.5 mL (0.5)
AMG 145 140 mg Q2W	2.0 mL (0.5 + 0.5 + 0.5 + 0.5)	None
Placebo Q4W	None	6 mL (1 + 1 + 1 + 1 + 1 + 1)
AMG 145 280 mg Q4W	4 mL (1 + 1 + 1 + 1)	2 mL (1 + 1)
AMG 145 350 mg Q4W	5 mL (1 + 1 + 1 + 1 + 1)	1 mL (1)
AMG 145 420 mg Q4W	6 mL (1 + 1 + 1 + 1 + 1 + 1)	None

Q2W = every 2 weeks; Q4W = every 4 weeks.
[a] Each sterile vial of AMG 145 contained a 1 mL deliverable volume of 70 mg/mL AMG 145.

The manufacturing batch numbers for AMG 145 are provided in Listing 14-8.9.1.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo was provided in containers identical to those for AMG 145 as a clear, colorless, sterile, frozen liquid. Placebo was composed of AMG 145 excipients. Placebo was administered SC Q2W or Q4W according to the randomized group assignment. The manufacturing batch numbers for placebo are provided in Listing 14-8.9.1.

Ezetimibe 10 mg tablets were administered orally once daily for 12 weeks as described in the ZETIA® [ezetimibe] package insert. The manufacturing batch numbers for ezetimibe are provided in Listing 14-8.9.1.

Duration of Treatment: Subjects received AMG 145, placebo, or ezetimibe for 12 weeks.

Study Endpoints:

The primary efficacy endpoint was the percent change from baseline in LDL-C at week 12.

The secondary efficacy endpoints were:

- absolute change from baseline in LDL-C at week 12.
- percent change from baseline in non-HDL-C at week 12.
- percent change from baseline in ApoB at week 12.
- percent change from baseline in the total cholesterol/HDL-C ratio at week 12.
- percent change from baseline in ApoB/ApoA1 ratio at week 12.

Safety endpoints were:

- subject incidence of treatment emergent adverse events.
- safety laboratory values and vital signs at each scheduled visit.
- electrocardiogram parameters (such as PR, QRS, QT and QTc intervals) at each scheduled visit.
- incidence of anti-AMG 145 antibody (binding and neutralizing) formation.

Pharmacokinetics endpoints were:

- serum concentration of AMG 145 and PCSK9 at selected time points.
- time of the maximum concentration (t_{max}), maximum concentration (C_{max}), minimum concentration (C_{min}), and area under the curve (AUC) obtained between weeks 8 to 12 (PK parameter endpoints from the PK substudy)
- area under the unbound serum PCSK9-effect curve ($AUEC_{PCSK9}$), lowest unbound serum PCSK9 concentration attained ($C_{min,\ PCSK9}$), time at which the lowest PCSK9 was observed ($T_{min,\ PCSK9}$)
- area under the LDL-C-effect curve (AUEC), lowest LDL-C concentration attained ($C_{min,\ LDL\text{-}C}$), time at which the lowest LDL-C was observed ($T_{min,\ LDL\text{-}C}$), average LDL-C between weeks 8 and 12 ($LDL\text{-}C_{,\ substudy\ avg}$), week 12 LDL-C ($LDL\text{-}C_{,\ substudy\ W12}$), and the starting baseline LDL-C (calculated LDL-C parameter endpoints from the PK substudy)

[redacted]

Statistical Methods:

General Considerations

Summary statistics for continuous variables included the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. For categorical variables, the frequency and percentage were provided.

[redacted]

All primary and secondary endpoint analyses of LDL-C used ultracentrifugation (UC) LDL-C, if available. For the exploratory endpoints and longitudinal analyses, calculated LDL-C was used.

Analyses of Primary Endpoint

The treatment effects of AMG 145 were assessed for the 2 dose frequency groups separately and the doses within each dose frequency group as follows: (1) the treatment effects of various AMG 145 doses administered Q2W compared with placebo, and (2) the treatment effects of various AMG 145 doses administered Q4W compared with placebo. A type I error of 0.05 was used for testing within each dose-frequency group.

For each dosing frequency, the primary efficacy endpoint of percent change in LDL-C from baseline at week 12 was analyzed using an analysis of covariance (ANCOVA) model to assess the efficacy of each AMG 145 dose group to placebo. The ANCOVA model included terms for the treatment group and stratification factor. The efficacy of AMG 145 was evaluated by using a hierarchical sequential testing approach to control the family-wise error rate for multiple comparisons at ≤ 0.05. The highest AMG 145 dose was compared with placebo using the 0.05 significance level. If the highest AMG 145 dose reached statistical significance, then the next highest dose was assessed. Testing of the doses continued in descending strength until the 0.05 statistical significance was not met or the lowest dose within the dosing frequency was tested, whichever occurred first.

Analyses of Secondary Endpoints

Primary analysis of the secondary endpoints of change and percent change from baseline was similar to the primary analysis for the primary endpoint. No multiplicity adjustment was made for secondary and other non-primary endpoints.

Safety Analyses

Adverse events were coded using Medical Dictionary for Regulatory Activities version 14.1. All adverse events were summarized by treatment group assigned at randomization. The subject incidence of adverse events was summarized for all treatment emergent, serious, treatment related, and serious treatment related events and those leading to withdrawal of IP by system organ class and preferred term in descending order of frequency. Summaries of treatment emergent, serious, treatment related, and serious treatment related adverse events occurring in at least 5% of subjects by preferred term in any treatment arm were provided in descending order of frequency. Subgroup analyses for stratification factor, age group (< 65, ≥ 65), sex, and race (if appropriate) were presented by system organ class and preferred term in descending order of frequency. All races with less than 5% of the total enrolled subjects were pooled together for summary purposes. Measurements of laboratory, ECGs, and vital signs were summarized over time. Lab shift tables were provided.

Summary of Results:

Subject Disposition: A total of 411 subjects were randomized. Overall, 274 subjects were randomized to 1 of the 6 AMG 145 groups (45 were randomized to receive 70 mg Q2W and 140 mg Q2W; and 46 were randomized to receive 105 mg Q2W, 280 mg Q4W, 350 mg Q4W, and 420 mg Q4W), 46 subjects were randomized to receive placebo Q2W, 45 subjects were randomized to receive placebo Q4W, and 46 subjects were randomized to receive ezetimibe. A total of 406 (98.8%) subjects received IP (271 AMG 145, 45 ezetimibe, and 90 placebo) and were included in the Full Analysis Set. A total of 397 subjects (96.6%) completed the study.

Baseline Demographics:

Sex: 34.2% of subjects were male; 65.8% of subjects were female

Age: 50.6 (11.8) years

Ethnicity: 86.2% not Hispanic or Latino; 13.8% Hispanic or Latino

Race: 78.6% of subjects were white, 15.8% of subjects were black, 4.2% of subjects were Asian, 0.7% of subjects were American Indian or Alaska native, 0.5% of subjects were native Hawaiian or other Pacific Islander, and 0.2% of subjects were “other”

Efficacy Results: Results of the primary efficacy analysis showed statistically significant reductions in the percent change from baseline in UC LDL-C at week 12 relative to placebo for all AMG 145 treatment groups within both the Q2W and Q4W dosing frequencies ($p < 0.001$). The percent reduction in UC LDL-C was dose-dependent within each AMG 145 dosing frequency (Q2W and Q4W). The largest percent reductions were observed at the highest dose within each dosing frequency (ie, 140 mg Q2W and 420 mg Q4W). Percent reductions relative to placebo ranged from 37% (70 mg) to 47% (140 mg) in the Q2W groups and from 44% (280 mg) to 53% (420 mg) in the Q4W groups. Reductions in LDL-C occurred early in the treatment period and were sustained through week 12 in all AMG 145 groups. Least squares mean LDL-C percent reductions from baseline at week 12 ranged from 41% to 51% in the AMG 145 Q2W groups and from 39% to 48% in the AMG 145 Q4W groups compared with a 4% reduction in the Q2W placebo group and a 5% increase in the Q4W placebo group.

Sensitivity analyses confirmed the results of the primary efficacy analysis. Subgroup analysis (by stratification factor and each baseline covariate) showed reductions in the percent change from baseline in UC LDL-C at week 12 relative to placebo for each of the AMG 145 groups within both the Q2W and Q4W dosing frequencies. Analyses adjusting for each of the covariates in the primary analysis ANCOVA model showed results that were consistent with the primary analysis.

Results of exploratory analyses on the primary efficacy endpoint showed statistically significant reductions in the percent change from baseline in UC LDL-C at week 12 compared with ezetimibe in all AMG 145 treatment groups within both the Q2W and Q4W dosing frequencies ($p < 0.001$), with percent reductions relative to ezetimibe ranging from 27% (70 mg) to 37% (140 mg) in the Q2W groups and from 25% (280 mg) to 34% (420 mg) in the Q4W groups.

Analyses of secondary efficacy endpoints showed dose-dependent, statistically significant ($p < 0.001$) reductions relative to placebo and relative to ezetimibe for all AMG 145 groups within both the Q2W and Q4W dosing frequencies for each of the key secondary efficacy endpoints (absolute change from baseline in UC LDL-C at week 12 and percent change from baseline in non-HDL-C, ApoB, total cholesterol/ HDL-C ratio, and ApoB/ApoA1 ratio at week 12). For each of the key secondary efficacy endpoints, decreases were dose-dependent within each AMG 145 dosing frequency (Q2W and Q4W), with the largest decreases observed at the highest dose within each dosing frequency (ie, 140 mg Q2W and 420 mg Q4W). Regarding the other key lipid parameters, treatment with AMG 145 resulted in statistically significant ($p \leq 0.05$) reductions relative to placebo for all AMG 145 groups within both the Q2W and Q4W dosing frequencies (unless noted) for percent change from baseline at week 12 in total cholesterol, VLDL-C (except 280 mg and 350 mg), and Lp(a) and for observed PCSK9 at week 12. Treatment with AMG 145 also consistently elevated HDL-C; increases in the 105 mg Q2W and 140 mg Q2W groups were statistically significant relative to placebo. Statistically significant increases in ApoA1 relative to placebo were also observed at week 12 for all AMG 145 dose groups except the lowest within each dose frequency (70 mg Q2W and 280 mg Q4W). Triglyceride values were reduced relative to placebo for all AMG 145 groups within both the Q2W and Q4W dosing frequencies but did not reach statistical significance in any group. With few exceptions, the effect of AMG 145 on these other key lipid parameters was dose-dependent, with the greatest reductions or increases occurring in the highest AMG 145 dose group within each dosing frequency (ie, 140 mg Q2W and 420 mg Q4W).

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Pharmacokinetic Results: Results from the PK substudy indicated that exposure increased with increasing dose and was approximately linear for doses ≥ 140 mg SC. Twelve weeks of AMG 145 administration resulted in AMG 145 serum concentrations that approached steady-state. The t_{max} occurred approximately 1 week following SC administration.

Excursions in PCSK9 were observed in both the Q2W and Q4W regimens and were characterized by a return towards baseline at the end of the dosing interval. As expected from a regimen with more frequent dosing, the Q2W regimens resulted in less maximal PCSK9 lowering but also less rise towards baseline at the end of the doing interval. The 140 mg Q2W regimen was associated with a maximum reduction to less than 50 ng/mL and was able to maintain the mean PCSK9 at approximately 100 ng/mL at the end of the dosing interval. In contrast, the Q4W regimens were associated with near complete suppression at the time of greatest effect but returned to approximately 150 ng/mL at the end of the dosing interval. These changes were consistent with the decline in AMG 145 serum concentrations over the dose interval. The median observed maximum lowering ($T_{min, PCSK9}$) over weeks 8 to 12 occurred 1 week after dosing. The mean calculated PCSK9 concentrations at the observed nadir of PCSK9 ($C_{min, PCSK9}$) were 14.1 ng/mL for the 140 mg Q2W group and were undetectable in the 420 mg Q4W group. The time-averaged reduction in PCSK9 as characterized by the area under the PCSK9 concentration time curve generally exhibited dose-dependent increases in PCSK9 lowering.

In the PK substudy, the AUEC was estimated in order to assess the time-averaged LDL-C lowering. Consistent with the PK, a dose-dependent increase in the mean calculated LDL-C AUEC was observed in both the Q2W and Q4W regimens. Mean calculated LDL-C AUEC values in the Q2W regimens were 1710 day•mg/dL in the 70 mg Q2W group, 2260 day•mg/dL in the 105 mg Q2W group, and 2340 day•mg/dL in the 140 mg Q2W group. Similarly, the mean calculated LDL-C AUEC values in the Q4W regimens were 2010 day•mg/dL in the 280 mg Q4W group, 2070 day•mg/dL in the 350 mg Q4W group, and 2460 day•mg/dL in the 420 mg Q4W group. In subjects receiving AMG 145 monotherapy, the greatest reduction was achieved after 140 mg Q2W or 420 mg Q4W. The maximum LDL-C lowering effect of AMG 145 was not attained at the end of the dosing interval with these dosing regimens; the mean calculated LDL-C percent changes from baseline at the observed nadir of LDL-C lowering ($C_{min, LDL-C}$) were -71% for both the 140 mg Q2W and the 420 mg Q4W regimens. By week 12, the calculated LDL-C

percent changes from baseline were -59% and -54%, respectively. The estimated mean average LDL-C percent changes from baseline between weeks 8 and 12 for both the 140 mg Q2W and the 420 mg Q4W regimens were -63%. The week 12 return in calculated LDL-C was consistent with the return in PCSK9 towards baseline. Calculated LDL-C concentrations obtained in the PK substudy at week 12 were similar to those from all subjects in the overall study.

The mean calculated absolute LDL-C values at the observed nadir for both the 140 Q2W and 420 Q4W regimens ($C_{min,\ LDL\text{-}C}$) were 41 mg/dL. By week 12, the LDL-C was returning toward baseline, which was consistent with the decline in AMG 145 serum concentrations. The observed LDL-C, $_{substudy\ W12}$ values were 58 mg/dL and 64 mg/dL for the 140 mg Q2W and 420 Q4W regimens, respectively. The LDL-C, $_{substudy\ avg}$ values during weeks 8 to 12 were estimated to be 51 mg/dL and 52 mg/dL for the 140 mg Q2W and 420 Q4W regimens, respectively.

Anti-AMG 145 Antibody Results: Of the 269 subjects in the AMG 145 treatment groups with a post-baseline result, 1 subject (0.4%) in the AMG 145 105 mg Q2W group tested positive for anti-AMG 145 binding antibodies (negative for neutralizing antibodies) at day 29. This result was not confirmed at EOS where the subject tested negative for anti-AMG 145 antibodies; this subject received all IP per protocol. Of the 83 subjects in the placebo groups with a post-baseline result, 1 subject (1%) in the Q4W placebo group tested positive for binding antibodies (negative for neutralizing antibodies) at the EOS.

Safety Results: Overall, 203 (50%) subjects experienced at least 1 treatment emergent adverse event. Treatment emergent adverse events were reported in 136/271 (50.2%) subjects receiving AMG 145, 26/45 (57.8%) subjects receiving ezetimibe, and 41/90 (45.6%) subjects receiving placebo. The 3 most commonly reported adverse events in the AMG 145 group (AMG 145; ezetimibe; placebo) were upper respiratory tract infection (6.3%; 11.1%; 7.8%), nasopharyngitis (4.1%; 11.1%; 3.3%), and diarrhea (3.7%; 2.2%; 3.3%). There did not appear to be a relationship between the subject incidence of treatment emergent adverse events and the dose or dosing frequency of AMG 145.

Treatment related adverse events were reported in 31/271 (11.4%) subjects receiving AMG 145, 3/45 (6.7%) subjects receiving ezetimibe, and 8/90 (8.9%) subjects receiving placebo. The 3 most commonly reported treatment related adverse events in the AMG 145 group (AMG 145; ezetimibe; placebo) were injection site induration (1.8%; 0; 0), myalgia (1.8%, 0; 0), and fatigue (1.5%; 2.2%; 2.2%).

Nine (2.2%) subjects experienced grade 3 adverse events and 2 (0.5%) subjects experienced grade 4 adverse events. All adverse events ≥ grade 3 were single occurrences and were balanced across treatments: AMG 145 (7/271 [2.6%]), ezetimibe (2/45 [4.4%]), and placebo (2/90 [2.2%]). Grade 4 events were immunoglobulin A (IgA) nephropathy (AMG 145 105 mg Q2W) and increased creatine phosphokinase (AMG 145 420 mg Q4W); neither was considered related to IP by the investigator.

No deaths occurred during the study. Serious adverse events were reported in 3 (0.7%) subjects: grade 3 appendicitis in 1 subject in the AMG 145 140 mg Q2W group, grade 4 IgA nephropathy in 1 subject in the AMG 145 105 mg Q2W group, and grade 3 humerus fracture in 1 subject in the AMG 145 350 mg Q4W group.

Two subjects in the placebo group and no subjects in the AMG 145 group had an adverse event that led to discontinuation of IP.

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There were no trends indicative of clinically important adverse effects of AMG 145 on selected laboratory variables, ECGs, or vital signs.

Conclusions: Treatment with AMG 145 as monotherapy resulted in statistically significant, dose-dependent reductions in the percent change from baseline at week 12 in LDL-C relative to placebo at all doses tested ($p < 0.001$). Percent reductions were dose-dependent within each dosing frequency (Q2W and Q4W), with the largest percent reductions at the highest dose within each dosing frequency. Percent reductions from baseline relative to placebo at week 12 for the 140 mg Q2W and 420 mg Q4W dose groups were 47% and 53%, respectively. Treatment with AMG 145 also resulted in statistically significant reductions in the percent change in LDL-C at all

doses tested ($p < 0.001$) compared with ezetimibe alone. The greatest effects were observed in the 140 mg Q2W and 420 mg Q4W AMG 145 dose groups with decreases of 37% and 34%, respectively, at week 12 compared with ezetimibe. Treatment with AMG 145 as monotherapy also resulted in dose-dependent, statistically significant reductions relative to placebo and relative to ezetimibe for all AMG 145 groups within both the Q2W and Q4W dosing frequencies for each of the key secondary efficacy endpoints (absolute change from baseline in UC LDL-C at week 12 and percent change from baseline in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ApoA1 ratio at week 12). Results from the PK substudy indicated that exposure increased with increasing dose and was approximately linear for doses ≥ 140 mg SC. Excursions in PCSK9 were observed in both the Q2W and Q4W regimens and were characterized by a return towards baseline at the end of the dosing interval. As expected from AMG 145 regimens with more frequent dosing, the Q2W regimens resulted in less maximal PCSK9 lowering but also less rise towards baseline at the end of the dosing interval. The time-averaged reduction in PCSK9 as characterized by the area under the PCSK9 concentration time curve generally exhibited dose-dependent increases in PCSK9 lowering. Consistent with AMG 145 PK and PCSK9, a dose-dependent increase in the mean calculated LDL-C AUEC in both the Q2W and Q4W regimens was observed. The estimated mean average LDL-C percent changes from baseline between weeks 8 and 12 for both the 140 mg Q2W and the 420 mg Q4W groups were -63% demonstrating that, of the doses studied, these 2 regimens produced equivalent and the greatest amount of LDL-C lowering. These data also indicated that the maximum LDL-C lowering effect of AMG 145 was likely observed, but as expected based on the biology, not fully sustained over the dosing interval with these regimens. Treatment with AMG 145 in this setting did not result in any clinically significant safety findings. The overall subject incidence of treatment emergent adverse events was higher in AMG145 groups compared with placebo. There was no relationship between the subject incidence of treatment emergent adverse events and the dose or dosing frequency of AMG 145. [redacted]