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, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C, Compared with Ezetimibe, in Hypercholesterolemic Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor (GAUSS: **G**oal **A**chievement after **U**tilizing an anti-PCSK9 antibody in **S**tatin Intolerant **S**ubjects)

Investigator(s) and Study Center(s): This study was conducted at 33 centers in Australia, Belgium, Canada, Denmark, Finland, Spain, Sweden, and the United States. A list of investigators is provided in Appendix 4.

Publication(s): None at the time this report was written.

Study Period: 28 July 2011 (date first subject enrolled) to 08 May 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. This study was designed to evaluate the safety and efficacy of AMG 145 compared with ezetimibe in subjects with hypercholesterolemia who are intolerant to an effective dose of a HMG-CoA reductase inhibitor (ie, statin).

The primary objective of the study was to evaluate the effect of 12 weeks of subcutaneous (SC) AMG 145 compared with ezetimibe on percent change from baseline in low density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor.

The secondary objectives were:

- To evaluate the safety and tolerability of 3 doses of AMG 145 SC alone, a high dose of AMG 145 SC with ezetimibe, or ezetimibe alone in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor.
- To assess the effects of 12 weeks of AMG 145 SC alone, AMG 145 SC with ezetimibe, or ezetimibe alone 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 hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor.
- To characterize the pharmacokinetics (PK) of AMG 145 following SC injection in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor.

Exploratory objectives are listed in Section 6.3.

Methodology:

This was a phase 2, multicenter, randomized, double-blind, placebo- and ezetimibe-controlled study to evaluate the tolerability and efficacy of AMG 145 compared with ezetimibe in subjects with hypercholesterolemia unable to tolerate an effective dose of a HMG-CoA reductase inhibitor (ie, statin therapy). After a screening and placebo run-in period, eligible subjects were randomized equally to 1 of the following 5 treatment groups:

- AMG 145 280 mg SC every 4 weeks (Q4W)
- AMG 145 350 mg SC Q4W
- AMG 145 420 mg SC Q4W

- AMG 145 420 mg SC Q4W and ezetimibe 10 mg once daily (QD) by mouth (PO)
- Placebo SC Q4W and ezetimibe 10 mg QD PO

Randomization was stratified by screening LDL-C level (< 130 mg/dL [3.4 mmol/L] or ≥ 130 mg/dL) and statin use at baseline (yes or no). Subjects received the first of three 6 mL SC injections of investigational product (IP) at randomization (day 1) with 2 additional SC injections at weeks 4 and 8 and completed the study with an end-of-study visit and the last estimation of lipids at week 12. Safety and efficacy endpoints were collected at scheduled time points. Subjects agreeing to participate in the optional PK substudy made additional clinic visits during weeks 9, 10, and 11.

Number of Subjects Planned: 150 (30 subjects per treatment group)

Number of Subjects Enrolled: 160 subjects were randomized

Diagnosis and Main Criteria for Eligibility:

Males and females ≥ 18 to ≤ 75 years of age were eligible for this study. Subjects were either not to be on a statin or were to be on a low-dose statin (defined as a maximal total weekly dose of atorvastatin ≤ 70 mg, simvastatin ≤ 140 mg, pravastatin ≤ 140 mg, rosuvastatin ≤ 35 mg, lovastatin ≤ 140 mg, or fluvastatin ≤ 280 mg; for statins not listed previously, the maximal total weekly dose was defined as 7 times the smallest available tablet size). Subjects were not to be at LDL-C goal as evidenced by their National Cholesterol Education Program Adult Treatment Panel III risk category and the following LDL-C levels by central laboratory at screening:

- fasting LDL-C ≥ 100 mg/dL (2.6 mmol/L) (for subjects with diagnosed coronary heart disease [CHD] or who were CHD risk equivalent)
- fasting LDL-C ≥ 130 mg/dL (3.4 mmol/L) (for subjects without diagnosed CHD or who were risk equivalent and had 2 or more risk factors)
- fasting LDL-C ≥ 160 mg/dL (4.1 mmol/L) (for subjects without diagnosed CHD or who were risk equivalent and had 1 or no risk factors)

Subjects were to have a history of statin intolerance (must have tried at least 1 statin and been unable to tolerate any dose or an increased statin dose above the total weekly maximum doses listed in Section 4 of the protocol [Appendix 1] because of intolerable myalgia [muscle pain, soreness, weakness, or cramps] or myopathy [myalgia plus a raised creatine phosphokinase (CK)], with symptoms resolving or improving when the statin dose was decreased or discontinued). Fasting triglycerides were required to be ≤ 400 mg/dL (4.5 mmol/L) at screening.

Subjects were excluded if they had taken red yeast rice, niacin [> 200 mg/day], omega-3 fatty acids [> 1000 mg/day]), or prescription lipid regulating drugs (eg, fibrates and derivatives) other than statins, ezetimibe, bile-acid sequestering resin, or stanols and stanol esters in the 6 weeks prior to LDL-C screening. Other major exclusions included New York Heart Association class III or IV heart failure; last known left ventricular ejection fraction < 30%; or uncontrolled serious cardiac arrhythmia, myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft, or stroke in the 3 months prior to randomization.

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. Each sterile vial was filled with 1 mL deliverable volume of 70 mg/mL AMG 145 formulated with [redacted]. AMG 145 was administered SC to assigned groups at doses of 280, 350, or 420 mg Q4W in vials of 6 mL, as described below, to achieve the assigned dosing concentration. In order to maintain blinding, AMG 145 and placebo were administered as follows:

Treatment Arm	Total AMG 145 (70 mg/mL) Volume (volume extracted per vial, mL)	Total Placebo Volume (volume extracted per vial, mL)
Placebo Q4W + Ezetimibe	None	6 mL (1.0 + 1.0 + 1.0 + 1.0 + 1.0 + 1.0)
AMG 145 280 mg Q4W	4 mL (1.0 + 1.0 + 1.0 + 1.0)	2 mL (1.0 + 1.0)
AMG 145 350 mg Q4W	5 mL (1.0 + 1.0 + 1.0 + 1.0 + 1.0)	1 mL (1.0)
AMG 145 420 mg Q4W	6 mL (1.0 + 1.0 + 1.0 + 1.0 + 1.0 + 1.0)	None
AMG 145 420 mg Q4W + ezetimibe	6 mL (1.0 + 1.0 + 1.0 + 1.0 + 1.0 + 1.0)	None

Q4W = every 4 weeks.

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 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 PO QD 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 underwent a screening/placebo run-in period of up to 6 weeks followed by a 12 week treatment period for a maximal study duration of 18 weeks.

Study Endpoints:

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

The secondary 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

In addition, percent changes from baseline at week 12 in HDL-C, very low density lipoprotein cholesterol (VLDL-C), triglycerides, total cholesterol, ApoA1, and lipoprotein(a) (Lp(a)) and observed PCSK9 at week 12 were identified as other indicators of efficacy and were analyzed in the same manner as the secondary endpoints defined above.

The safety endpoints were:

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

The PK endpoints were:

- serum concentrations of AMG 145 and PCSK9 at select time points
- AMG 145 time to maximal concentration (t_{max}), AMG 145 maximal concentration (C_{max}), and AMG 145 area under the concentration-time curve obtained between weeks 8 to 12 ($AUC_{week8-12}$)
- area under the unbound serum PCSK9-effect curve ($AUEC_{PCSK9}$), lowest unbound serum PCSK9 concentration attained ($C_{min, PCSK9}$), and time at which the lowest PCSK9 was observed ($T_{min, PCSK9}$)
- area under the LDL-C-effect curve (AUEC), lowest LDL-C concentration attained ($C_{min, LDL-C}$), the time at which the lowest LDL-C was observed ($T_{min, LDL-C}$), 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 (SD) or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. For categorical variables, the frequency and percentage were given.

[redacted]

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

Analyses of Primary Endpoint

For the primary endpoint of percent change in LDL-C from baseline at week 12, the efficacy of AMG 145 was evaluated using a hierarchical sequential testing approach to control the family-wise error rate for multiple comparisons at ≤ 0.05.

The primary efficacy endpoint used an analysis of covariance (ANCOVA) model to assess the efficacy of each AMG145 dose group to ezetimibe alone. The ANCOVA model included terms for the treatment group (AMG 145 dose groups alone and ezetimibe alone) and stratification factors. 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 was tested, whichever occurred first.

Analyses of Secondary and Exploratory Endpoints

Analyses of the secondary endpoints of change and percent change from baseline were similar to the primary analysis for the primary endpoint; no multiple comparison adjustment was implemented, and all tests were based on a significance level of 0.05.

Exploratory lipid-related endpoints did not use missing data imputation and were summarized by treatment group and scheduled visit using descriptive statistics.

Safety Analyses

The Medical Dictionary for Regulatory Activities version 15.0 was used to code all adverse events to a system organ class and preferred term. Adverse events were summarized by treatment group. The subject incidence of all treatment emergent, serious, treatment related, and serious

and treatment related adverse events, and those leading to withdrawal of IP, were summarized 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 the subjects by preferred term in any treatment arm were provided in descending order of frequency. Subgroup analyses for stratification factors (LDL-C < 130 mg/dL or ≥ 130 mg/dL), age group (< 65, ≥ 65), sex, and race (if appropriate) were presented by system organ class and preferred term in descending order of frequency. For reporting purposes, all races with less than 5% of the total enrolled subjects were pooled together for summary purposes. Measurements of laboratory findings, ECGs, and vital signs were summarized over time. Lab shift tables were provided.

Summary of Results:

Subject Disposition: A total of 160 subjects were randomized. Overall, 96 subjects were randomized to 1 of the 3 AMG 145 Q4W alone groups (32 subjects in each AMG 145 alone group), 31 subjects were randomized to receive AMG 145 420 mg Q4W + ezetimibe, and 33 subjects were randomized to receive placebo Q4W + ezetimibe. A total of 157 (98.1%) subjects received IP and a total of 155 (96.9%) subjects completed the study.

Baseline Demographics:

Sex: 36.3% of subjects were male; 63.7% of subjects were female

Mean Age (SD): 61.8 (8.4) years

Ethnicity: 98.7% not Hispanic or Latino; 1.3% Hispanic or Latino

Race: whites (88.5%) made up the majority of the population followed by blacks and Asians (5.1% each) and native Hawaiian or other Pacific Islander, Japanese, and other (< 1% each)

Efficacy Results:

Results of the primary efficacy analysis showed statistically significant, dose-dependent reductions in the percent change from baseline in UC LDL-C at week 12 relative to the placebo + ezetimibe group for all AMG 145 alone treatment groups ($p < 0.001$). Percent reductions relative to the placebo + ezetimibe group (treatment difference) were 26%, 28%, and 36% for the AMG 145 280, 350, and 420 mg alone groups, respectively. 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 reduction from baseline at week 12 was 41% for AMG 145 280 mg, 43% for AMG 145 350 mg, and 51% for AMG 145 420 mg alone groups compared with a 15% reduction in the placebo + ezetimibe group.

A statistically significant reduction (treatment difference of 47%) in the percent change from baseline in UC LDL-C at week 12 was also observed for the AMG 145 + ezetimibe group compared with the placebo + ezetimibe group ($p < 0.001$).

Sensitivity analyses confirmed the results of the primary 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 the placebo + ezetimibe group for most of the AMG 145 alone groups and for the AMG 145 + ezetimibe group. Analyses adjusting for each of the covariates in the primary analysis ANCOVA model showed results that were consistent with the primary analysis.

Analyses of secondary efficacy endpoints showed dose-dependent, statistically significant ($p < 0.001$) reductions relative to the placebo + ezetimibe group for all AMG 145 alone groups and for the AMG 145 + ezetimibe group for each of the 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). Regarding the other indicators of efficacy (HDL-C, VLDL-C, triglycerides, total cholesterol, ApoA1, Lp(a), and PCSK9), treatment with AMG 145 resulted in statistically significant ($p \leq 0.05$) reductions relative to placebo + ezetimibe for all AMG 145 alone groups for percent change from baseline at week 12 in total cholesterol and Lp(a) and for observed PCSK9 at week 12. Treatment with AMG 145 in all AMG 145 alone groups also consistently elevated HDL-C compared to the placebo + ezetimibe group; results were statistically significant for the AMG 145 420 mg alone group. Statistically significant increases in ApoA1 relative to the placebo + ezetimibe group were also

observed at week 12 for all AMG 145 alone groups. Reductions in triglycerides and VLDL-C relative to the placebo + ezetimibe group were noted but were not statistically significant in any group. Treatment with AMG 145 + ezetimibe resulted in statistically significant ($p \leq 0.05$) reductions relative to placebo + ezetimibe for percent change from baseline at week 12 in total cholesterol, HDL-C, VLDL-C, and Lp(a) and for observed PCSK9 at week 12. No treatment difference between the AMG 145 + ezetimibe group and the placebo + ezetimibe group was noted for percent change from baseline at week 12 in triglycerides. Treatment with AMG 145 + ezetimibe resulted in a statistically significant increase from baseline in ApoA1 of 9% relative to placebo + ezetimibe for percent change at week 12.

[redacted]

Pharmacokinetic Results:

Noncompartmental analysis of AMG 145 PK and pharmacodynamic data indicate that statin-intolerant subjects receiving AMG 145 in the PK substudy had dose-dependent AMG 145 exposure and robust lowering of PCSK9 and LDL-C. Linear increases in AMG 145 PK were observed across the AMG 145 280, 350, and 420 mg alone groups and the C_{max} occurred 1 week following AMG 145 administration. These AMG 145 PK observations were consistent with previously reported results from other phase 1a and phase 2 studies. Treatment with AMG 145 resulted in lowering of mean PCSK9 to near complete suppression in all treatment groups at the peak effect and was associated with maintaining PCSK9 suppression below baseline by week 12. These regimens resulted in mean maximum absolute calculated LDL-C values ranging from 60 to 82 mg/dL. Average calculated LDL-C reductions as measured by the calculated LDL-C AUEC between weeks 8 and 12 were dose-dependent ranging from a mean of 2670 day•mg/dL in the AMG 145 280 mg alone group to a mean of 3680 day•mg/dL in the AMG 145 420 mg alone group. The PK substudy data support the selection of an AMG 145 420 mg SC dose regimen to provide maximum reduction in LDL-C in this population. An AMG 145 420 mg + ezetimibe regimen produced a slightly greater mean average calculated LDL-C AUEC (3830 day•mg/dL) compared to AMG 145 420 mg alone, consistent with the additional effect of ezetimibe.

Anti-AMG 145 Results:

A total of 154 subjects were tested for anti-AMG 145 antibodies and no subjects tested positive for anti-AMG 145 binding antibodies at either baseline or post-baseline time points.

Safety Results:

Overall, 94 (59.9%) subjects experienced at least 1 treatment emergent adverse event. The incidence of treatment emergent adverse events in subjects receiving AMG 145 alone (57.9%, 55/95) was lower compared to subjects receiving AMG 145 + ezetimibe (66.7%, 20/30) and comparable to the incidence in subjects receiving placebo + ezetimibe (59.4%, 19/32). No apparent relationship was observed between the incidence of treatment emergent adverse events and the dose of AMG 145. Treatment emergent adverse events that occurred in ≥ 5% of all subjects were nasopharyngitis (8.3%) and myalgia (8.9%). The incidence of nasopharyngitis was lower in subjects receiving AMG 145 alone (5.3%, 5/95) compared to subjects receiving AMG 145 + ezetimibe (10.0%, 3/30) or placebo + ezetimibe (15.6%, 5/32). The incidence of myalgia was lower in subjects receiving AMG 145 alone (7.4%, 7/95) compared to subjects receiving AMG 145 + ezetimibe (20.0%, 6/30) and comparable to subjects receiving placebo + ezetimibe (3.1%, 1/32).

Treatment related adverse events were reported in 17.9% (17/95) of subjects receiving AMG 145 alone, 16.7% (5/30) of subjects receiving AMG 145 + ezetimibe, and 21.9% (7/32) of subjects receiving placebo + ezetimibe. No apparent relationship was observed between the subject incidence of treatment related adverse events and the dose of AMG 145. The most commonly reported treatment related adverse event (occurring in ≥ 5% of subjects overall) was myalgia, which occurred in 6.3%, 6.7%, and 3.1% of subjects in the AMG 145 alone, AMG 145 + ezetimibe, and placebo + ezetimibe groups, respectively.

Seven (4.5%) subjects experienced Common Terminology Criteria for Adverse Events (version 4.0) grade 3 adverse events and 3 (1.9%) subjects experienced grade 4 adverse events.

All adverse events ≥ grade 3 were single occurrences. Across treatments these were AMG 145 280 mg alone (4/32 [12.5%]), AMG 145 420 mg alone (1/32 [3.1%]), and AMG 145 + ezetimibe (2/30 [6.7%]). Grade 4 events were increased blood CK, myositis, and syncope. All grade 4 events occurred in subjects in the AMG 145 350 mg alone group.

No deaths occurred during the study. Serious adverse events were reported in 4 (2.5%) subjects, all in the AMG 145 alone groups. Serious adverse events included coronary artery disease (1 subject, AMG 145 420 mg alone group), acute pancreatitis (1 subject, AMG 145 280 mg alone group), femoral neck fracture (1 subject, AMG 145 280 mg alone group), and syncope (1 subject, AMG 145 350 mg alone group). The serious adverse event of coronary artery disease was a coronary angiography and stenting procedure that was scheduled prior to enrollment into the study, without signs or symptoms of instability after enrollment.

Overall, 5 (3.2%) subjects experienced adverse events leading to discontinuation of IP, including 2 subjects in the AMG 145 alone groups, 1 subject in the AMG 145 + ezetimibe group, and 2 subjects in the placebo + ezetimibe group.

[redacted]

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

No risk was identified based on evaluation of the prespecified events of interest.

Conclusions:

Treatment with AMG 145 resulted in statistically significant, dose-dependent reductions in the percent change from baseline in UC LDL-C at week 12 relative to ezetimibe with percent reductions relative to ezetimibe ranging from 26% to 36% across the AMG 145 alone groups. Treatment with AMG 145 + ezetimibe also resulted in a statistically significant reduction (treatment difference of 47%) in the percent change from baseline in UC LDL-C at week 12 compared with ezetimibe alone (placebo + ezetimibe group), thus reflecting the additive effect of AMG 145 at a dose of 420 mg Q4W when added to other lipid lowering therapy. Dose-dependent, statistically significant reductions relative to ezetimibe for all AMG 145 alone groups and for the AMG 145 + ezetimibe group were observed for each of the defined 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). In the PK substudy, linear increases in AMG 145 PK were observed across the AMG 145 280, 350, and 420 mg alone groups and the C_{max} occurred 1 week following AMG 145 administration. Treatment with AMG 145 resulted in lowering of mean PCSK9 to near complete suppression in all treatment groups. Average calculated LDL-C reductions (LDL-C AUEC) between weeks 8 and 12 were dose-dependent. The PK substudy data support the selection of an AMG 145 420 mg SC dose regimen to provide maximum reduction in LDL-C in this population. Treatment with AMG 145 in this setting did not result in any clinically significant safety findings. Overall, the incidence of treatment emergent adverse events in subjects receiving AMG 145 alone was lower compared to subjects receiving AMG 145 + ezetimibe and comparable to subjects receiving placebo + ezetimibe. No apparent relationship was observed between the incidence of treatment emergent adverse events and the dose of AMG 145. [redacted]