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 Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Subjects with Heterozygous Familial Hypercholesterolemia

Investigator(s) and Study Center(s): This study was conducted at 24 centers in Asia, Canada, Europe, South Africa, and the United States. A complete listing of investigators is provided in Appendix 4.

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

Study Period: The first subject was enrolled on 02 August 2011 and the last patient completed their last visit on 16 May 2012.

Development Phase: 2

Introduction and Objectives:

Familial hypercholesterolemia is a rare disease caused by defects in the low-density lipoprotein receptor (LDLR) or its handling. In its heterozygous form, it affects about one in five hundred people, with higher rates among certain ethnic populations (Hobbs et al, 1987). When untreated, the cumulative risk of coronary heart disease (CHD) in patients with heterozygous familial hypercholesterolemia (HeFH) is high; 60% among men and more than 30% among women by the age of 60 (Slack, 1969; Stone et al, 1974; Austin et al, 2004).

Many patients with HeFH fail to reach their target lipid goal with statins and other add-on agents such as ezetimibe or niacin, resulting in an unmet medical need for more effective therapy in these patients.

AMG 145 is a fully human monoclonal immunoglobulin G2 that is being developed for the treatment of hypercholesterolemia as monotherapy or in combination with other dyslipidemia therapies. AMG 145 binds to the proprotein convertase subtilisin/kexin type 9 (PCSK9) and prevents the binding of PCSK9 with the hepatic LDLR. Because PCSK9 downregulates 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).

This study was designed to evaluate the tolerability, safety, and efficacy of 2 dosing regimens (350 and 420 mg) of AMG 145 administered subcutaneously (SC) once every 4 weeks (Q4W), compared with placebo, over a 12-week treatment period in subjects with HeFH.

The primary objective of this study was to evaluate the effect of 12 weeks of SC AMG 145, compared with placebo, on percent change from baseline in LDL-C in subjects with HeFH.

Secondary objectives of the study were:

- to evaluate the safety and tolerability of 2 doses of AMG 145 SC, compared with placebo, in subjects with HeFH
- to assess the effects of 12 weeks of AMG 145 SC, compared with 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 HeFH
- to characterize pharmacokinetics (PK) of AMG 145 after SC injection in subjects with HeFH

Exploratory objectives are listed in Section 6.3.

Methodology:

This was a phase 2, double-blind, randomized, placebo-controlled study designed to compare the efficacy and safety profile of AMG 145 versus placebo in subjects with HeFH. Eligible subjects completing the screening and placebo run-in periods were randomized equally to receive 3 doses of 1 of the following treatments:

- 350 mg AMG 145 SC Q4W
- 420 mg AMG 145 SC Q4W
- placebo SC Q4W

Randomization was stratified by screening LDL-C level (< 130 mg/dL [3.4 mmol/L] or ≥ 130 mg/dL) and ezetimibe use at baseline (yes or no). Randomized subjects were treated for 12 weeks and then underwent an end-of-study (EOS) follow-up visit, which completed the study. The study included collection of biomarker samples and all subjects were invited to participate in pharmacogenetic analyses. Subjects were also invited to participate in an optional PK substudy with 3 additional blood sampling visits scheduled at weeks 9, 10, and 11 to evaluate AMG 145 and PCSK9 concentrations. Investigators, site staff, subjects, and the study team were blinded to on-treatment lipid measurements.

Number of Subjects Planned: 150 (50 per treatment arm)

Number of Subjects Enrolled: 168 (56 placebo, 56 AMG 145 350 mg Q4W, and 56 AMG 145 420 mg Q4W)

Diagnosis and Main Criteria for Eligibility:

Men and women ≥ 18 to ≤ 75 years of age, with a diagnosis of HeFH by the diagnostic criteria of the Simon Broome Register Group (Scientific Steering Committee, 1991), fasting LDL-C of ≥ 100 mg/dL, and fasting triglycerides ≤ 400 mg/dL by central laboratory at screening were eligible for this study. Subjects had to be on stable dose(s) of a statin, with or without ezetimibe, for at least 4 weeks prior to screening.

Major exclusions were homozygous familial hypercholesterolemia and LDL or plasma apheresis within 12 months prior to randomization, use of prescription lipid-regulating drugs (other than statins or ezetimibe), or use of red yeast rice, niacin (> 200 mg/day), or omega-3 fatty acid (> 1,000 mg/day) for more than 2 weeks in the 3 months prior to screening.

A complete list of inclusion and exclusion criteria is provided in Section 7.5.

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 cohorts at doses of 350 mg or 420 mg Q4W in a total volume of 6 mL. In order to maintain blinding among the treatment cohorts, doses were split into several injections and administered as follows:

Treatment Cohort	Total AMG 145 (70 mg/mL) Volume (volume extracted per vial[a], mL)	Total Placebo Volume (volume extracted per vial, mL)
Placebo Q4W	None	6 mL (1 + 1 + 1 + 1 + 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

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 lot numbers of AMG 145 that were used in the study 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 comprised of AMG 145 excipients. Placebo was administered SC Q4W according to the randomized treatment assignment. The manufacturing lot numbers of placebo used in this study 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, resulting in maximum study duration of 18 weeks.

Study Endpoints:

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

Secondary Efficacy Endpoints:

- 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

Exploratory Efficacy Endpoints: Exploratory endpoints are presented in Section 7.10.3.3.

Safety Endpoints:

- 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

Pharmacokinetic Endpoints:

- serum concentration 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 from time 0 to the time of the last measurable concentration (AUC_t) obtained between weeks 8 to 12
- 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 ($C_{min, LDL-C}$), 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)

Statistical Methods:

General Considerations

Efficacy and safety analyses were performed on the full analysis set (FAS), which included all randomized subjects who received at least 1 dose of investigational product (IP). For all analyses, subjects were grouped according to their randomized treatment assignment.

In order to control for multiple comparisons to preserve the family-wise error rate of the primary analyses of the primary endpoint at ≤ 0.05, a Hochberg adjustment was utilized. Unless specified otherwise, all other hypothesis testing was 2-sided with a significance level of 0.05.

Analyses of Primary Endpoint

The treatment effects were assessed using an analysis of covariance (ANCOVA) model, with treatment group and stratification factors included in the model. A Hochberg adjustment for multiple comparisons was used to assess the treatment effect of each dose compared to placebo.

Missing values were imputed by using the last observation carried forward (LOCF) approach.

Analyses of Secondary and Exploratory Endpoints

Analyses of other endpoints were similar to the analysis of the primary endpoint; however, a significance level of 0.05 was used for all analyses. Comparisons among the AMG 145 dose groups were also performed for the primary, secondary, and additional endpoints.

[redacted]

Safety Analyses

Adverse events were coded using the Medical dictionary for regulatory activities (MedDRA), version 15. The subject incidence of treatment emergent adverse events, serious adverse events, treatment related adverse events and adverse events leading to discontinuation of investigational product was tabulated by system organ class and preferred term by randomized treatment group. Subgroup analyses (by stratification factors, age group, race, and gender, as appropriate) were presented for all adverse events.

Measurements of laboratory values, ECGs, and vital signs were summarized over time. Lab shift tables were provided.

Summary of Results:

Subject Disposition:

A total of 168 subjects were randomized at 24 study centers in the United States, Europe, Asia, Canada and South Africa. One-hundred twelve subjects were randomized to 1 of 2 AMG 145 groups (56 subjects each to 350 mg Q4W and 420 mg Q4W) and 56 subjects were randomized to placebo. A total of 167 (99.4%) subjects received investigational product, completed the study, and were included in the FAS.

Baseline Demographics:

Sex: 53.3% subjects were male; 46.7% of subjects were female

Age: Mean (SD) age of subjects was 49.6 (12.7) years

Ethnicity/Race: 88.6% of subjects were white, 4.2% were Asian, 2.4% were black, 0.6% were mixed race, and 4.2% were “other”. The majority of subjects (98.8%) were not of Hispanic/latino ethnicity.

Efficacy Results:

For the primary endpoint, statistically significant reductions in the percent change from baseline in UC LDL-C at week 12, relative to placebo, were observed for both the 350 mg and 420 mg AMG 145 treatment groups ($p < 0.001$) with treatment differences of 44% and 56%, respectively. Reductions in LDL-C were dose-dependent and greater in the AMG 145 420 mg group compared to the 350 mg group.

Sensitivity analyses confirmed the results of the primary efficacy analysis. Subgroup analysis (by stratification factor and each baseline covariate) showed greater reductions relative to placebo in the percent change from baseline in UC LDL-C at week 12 for both of the AMG 145 dose groups (350 mg and 420 mg Q4W). Analyses adjusting for each of the covariates in the primary analysis ANCOVA model showed results that were consistent with the primary analysis.

Pairwise comparisons between the AMG 145 350 mg and 420 mg groups showed a statistically significant difference in percent change from baseline in UC LDL-C at week 12 in favor of the 420 mg dose ($p<0.001$).

Treatment with AMG 145 also resulted in statistically significant ($p < 0.001$) reductions relative to placebo for both AMG 145 dose groups for most 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). Decreases for each of these secondary endpoints were dose-dependent, with the largest decreases observed in the 420 mg dose group. Decreases relative to placebo (treatment difference estimates) for the 350 mg

and 420 mg doses, respectively, were 65.5 mg/dL and 84.7 mg/dL (1.69 and 2.19 mmol/L) for absolute change from baseline in UC LDL-C at week 12; 42% and 53% for percent change from baseline at week 12 in non-HDL-C; 35% and 46% in ApoB; 37% and 45% in total cholesterol/HDL-C ratio; and 34% and 45% in ApoB/ApoA1 ratio.

For the other lipid parameters, treatment with AMG 145 resulted in statistically significant reductions relative to placebo in percent change from baseline at week 12 in both AMG 145 dose groups in total cholesterol ($p < 0.001$), very low density lipoprotein cholesterol (VLDL-C) ($p = 0.012$ [350 mg] and $p < 0.001$ [420 mg]), lipoprotein (a) [Lp(a)] ($p < 0.001$), triglycerides ($p = 0.008$ [350 mg] and $p < 0.001$ [420 mg]) and for observed PCSK9 ($p < 0.001$) at week 12. Decreases (AMG 145 350 mg and 420 mg) in total cholesterol (31% and 40%), VLDL-C (25% and 36%), Lp(a) (23% and 31%), and triglycerides (15% and 20%) were dose-dependent with a greater response for each parameter observed in the 420 mg dose group. Treatment with AMG 145 also resulted in statistically significant increases in HDL-C relative to placebo at week 12 in both dose groups; 8% ($p = 0.003$) in the 350 mg group and 7% ($p = 0.009$) in the 420 mg group. Statistically significant increases in ApoA1 relative to placebo at week 12 were not observed in either AMG 145 dose group ($p = 0.37$ and $p = 0.45$, respectively).

[redacted]

Pharmacokinetic Results:

Noncompartmental analysis of AMG 145 PK and PD data indicated that HeFH subjects receiving AMG 145 at 350 mg or 420 mg Q4W 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 350 mg and 420 mg Q4W regimens. C_{max} occurred 1 week following AMG 145 administration. Treatment with AMG 145 resulted in lowering of mean PCSK9 to near complete suppression in both treatment groups and was associated maintaining PCSK9 suppression below baseline by Week 12. The average calculated LDL-C reduction from baseline between weeks 8 and 12 in the PK substudy was 60% and 79% for the 350 mg and 420 mg Q4W regimens, respectively. This corresponded to an average absolute calculated LDL-C between weeks 8 and 12 of the study of 63.8 mg/dL and 28.9 mg/dL in these 2 dose groups. The 350 mg and 420 mg Q4W regimens resulted in mean maximum absolute calculated LDL-C reductions from baseline of 76% and 88%, respectively, about 2 weeks following a dose, which translated into absolute mean maximum calculated LDL-C values of 42 mg/dL and 17 mg/dL in the 2 regimens. The corresponding week 12 (trough) percent reductions from baseline for the 2 regimens were 44% and 68%, respectively. The mean calculated LDL-C $AUEC_{week8-12}$, a time-averaged LDL-C parameter, were 2630 day•mg/dL in the 350 mg Q4W group and 3040 day•mg/dL in the 420 mg Q4W group. The PK substudy data support the selection of a 420 mg SC dose regimen to provide maximum reduction in LDL-C in this population.

Anti-AMG 145 Results:

No binding or neutralizing antibodies were detected in subjects receiving AMG 145 or placebo.

Safety Results:

A total of 167 (99.4%) subjects received investigational product and were included in the FAS. Overall, 102 (61.1%) subjects experienced at least 1 treatment emergent adverse event.

Treatment emergent adverse events were reported in 58.2%, 66.1% and 58.9% of subjects in the AMG 145 350 mg Q4W group, AMG 145 420 mg Q4W, and placebo groups, respectively. The 3 most commonly reported treatment emergent adverse events in the AMG 145 group (combined AMG 145 groups; placebo) were nasopharyngitis (12.6%; 10.7%), injection site reaction (6.3%; 1.8%), and headache (5.4%; 8.9%). The most commonly reported treatment emergent adverse

events in the AMG 145 350 mg group (AMG 145 350 mg; AMG 145 420 mg; placebo) were nasopharyngitis (12.7%; 12.5%; 10.7%), injection site pain (9.1%; 3.6%; 1.8%), headache (5.5%; 5.4%; 8.9%), upper respiratory tract infection (5.5%; 3.6%; 0.0%), and sinusitis (5.5%; 1.8%; 1.8%). In the AMG 145 420 mg group, the 3 most commonly reported treatment emergent adverse events (AMG 145 350 mg; AMG 145 420 mg; placebo) were nasopharyngitis (12.7%; 12.5%; 10.7%), influenza (1.8%; 7.1%; 10.7%), and headache (5.5%; 5.4%; 8.9%). Nasopharyngitis, influenza and headache were also the 3 most commonly reported treatment emergent adverse events in the placebo group.

Treatment related adverse events were reported for 23.6% of subjects receiving AMG 145 350 mg, 14.3% of subjects receiving AMG 145 420 mg, and 10.7% of subjects receiving placebo. The 3 most commonly reported treatment related adverse events in the AMG 145 group (combined AMG 145 groups; placebo) were injection site pain (5.4%; 1.8%), headache (3.6%; 0.0%), and skin burning sensation (2.7%; 0.0%). The 3 most commonly reported treatment related adverse events in the AMG 145 350 mg group (AMG 145 350 mg; AMG 145 420 mg; placebo) were injection site pain (7.3%; 3.6%; 1.8%), headache (5.5%; 1.8%; 0.0%), and injection site erythema (3.6%; 0.0%; 0.0%). In the AMG 145 420 mg group, the most commonly reported treatment related adverse events (AMG 145 350 mg; AMG 145 420 mg; placebo) were injection site pain (7.3%; 3.6%; 1.8%) and skin burning sensation (1.8%; 3.6%; 0.0%). All other treatment related adverse events in this group were single occurrences. No treatment related adverse events were considered serious.

Seven (4.2%) subjects experienced NCI Common Terminology Criteria for AEs (CTCAE) grade 3 adverse events and 1 (0.6%) subject experienced a grade 4 adverse event. All adverse events ≥ grade 3 were single occurrences and were reported in 2 (3.6%) AMG 145 350 mg subjects, 4 (7.1%) AMG 145 420 mg subjects, and 1 (1.8%) placebo subject. The grade 4 event of increased blood creatinine kinase was reported in 1 (1.8%) subject in the AMG 145 420 mg group.

No deaths occurred during the study. Three serious treatment emergent adverse events (atrial fibrillation, appendicitis, and post-operative wound infection) were reported in 2 (1.2%) subjects, both in the AMG 145 420 mg Q4W group. None of the 3 serious adverse events were considered related to investigational product by the investigator.

Three subjects (1 AMG 145 350 mg, 1 AMG 145 420 mg, and 1 placebo) experienced adverse events that led to discontinuation of investigational product.

[redacted]

Evaluation of pre-specified adverse events of interest in this study did not lead to the identification of any risks.

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

Conclusions:

Treatment with AMG 145 (with or without statins and/or ezetimibe) in subjects with HeFH resulted in statistically significant reductions in the percent change from baseline at week 12 in UC LDL-C relative to placebo at both doses (350 mg and 420 mg Q4W) tested ($p < 0.001$). Percent reductions were dose-dependent with the greatest effects observed in the 420 mg dose group. Percent reductions from baseline relative to placebo at week 12 were 44% and 56%, respectively. Treatment with AMG 145 in this patient population also resulted in statistically significant reductions relative to placebo in both AMG 145 dose groups for most of the secondary 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) ($p < 0.001$).

AMG 145 PK and PD data indicated that HeFH subjects receiving AMG 145 at 350 mg or 420 mg Q4W 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 350 mg and 420 mg Q4W regimens. Treatment with AMG 145 resulted in near complete suppression PCSK9 in both treatment groups at peak effect and maintained PCSK9 suppression below baseline

(~ 350 mg/mL) through week 12. The average calculated LDL-C reduction from baseline in the PK substudy was 60% and 79% for the 350 mg and 420 mg Q4W regimens, respectively.

Treatment with AMG 145 in this patient population did not result in any clinically significant safety findings.

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