2. SYNOPSIS

Name of Sponsor: Amgen

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: LAPLACE - TIMI 57 - A Double-blind, Randomized, Placebo-controlled, Multicenter, Dose-ranging Study to Evaluate Tolerability and Efficacy of AMG 145 on LDL-C in Combination with HMG-CoA Reductase Inhibitors in Hypercholesterolemic Subjects (LAPLACE: **L**DL-C **A**ssessment w/ **P**CSK9 monoclona**L** **A**ntibody inhibition **C**ombined with statin th**E**rapy)

Investigators and Study Centers: This study was conducted at 78 centers in the United States, Canada, and Europe. Centers and principal investigators are listed in Appendix 4.

Publications: Kohli P, Desai NR, Giugliano RP, et al. Design and Rationale of the LAPLACE-TIMI 57 Trial: A Phase II, Double-Blind, Placebo-Controlled Study of the Efficacy and Tolerability of a Monoclonal Antibody Inhibitor of PCSK9 in Subjects With Hypercholesterolemia on Background Statin Therapy. *Clin Cardiol.* 2012;35:385-91.

Study Period: 18 July 2011 (date first subject enrolled) to 05 April 2012 (date last subject completed study)

Development Phase: 2

Objectives: AMG 145 is a fully human monoclonal IgG2 antibody 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 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 present study was designed to evaluate the safety and efficacy of AMG 145 administered once every 2 weeks (Q2W) or once every 4 weeks (Q4W), compared with placebo, in combination with a statin in subjects with hypercholesterolemia.

The primary objective was to evaluate the effect of 12 weeks of subcutaneous (SC) AMG 145 administered Q2W or Q4W, compared with placebo, on the percent change from baseline in LDL-C when used in addition to a statin in subjects with hypercholesterolemia.

The secondary objectives were:

- to evaluate the safety and tolerability of 6 dose regimens of AMG 145 SC, compared with placebo, when used in combination with a statin in subjects with hypercholesterolemia
- to assess the effects of 12 weeks of AMG 145 SC used in combination with a statin, compared with placebo used with a statin, 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 pharmacokinetics (PK) of AMG 145 following SC injection in subjects with hypercholesterolemia receiving statin therapy

Exploratory objectives are listed in Section 6.3.

Methodology: This phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study was designed to evaluate the efficacy and safety of 12 weeks of SC AMG 145 administered Q2W or Q4W, compared with placebo, in combination with a statin on the percent change from baseline in LDL-C in subjects with hypercholesterolemia. After a screening and placebo run-in period of up to 6 weeks, eligible subjects who were on stable dose(s) of statin therapy for at least 4 weeks with or without ezetimibe were randomized equally into 8 treatment groups to receive AMG 145 or placebo SC as detailed below. Randomization was stratified by screening LDL-C level (< 130 mg/dL vs ≥ 130 mg/dL) and ezetimibe use at baseline (yes/no).

Treatment Group	Investigational Product and Dose	Frequency	Planned N
1	AMG 145 70 mg	Q2W x 6	75
2	AMG 145 105 mg	Q2W x 6	75
3	AMG 145 140 mg	Q2W x 6	75
4	Placebo	Q2W x 6	75
5	AMG 145 280 mg	Q4W x 3	75
6	AMG 145 350 mg	Q4W x 3	75
7	AMG 145 420 mg	Q4W x 3	75
8	Placebo	Q4W x 3	75

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 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 visit occurred at week 12 for subjects randomized to the Q4W investigational product schedule and at week 14 for those subjects randomized to the Q2W investigational product 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: 600 (75 per treatment group for 8 treatment groups)

Number of Subjects Enrolled: 631 subjects were randomized

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men and women, ≥ 18 to ≤ 80 years of age, who were on a statin, with or without ezetimibe, with stable dose(s) for at least 4 weeks before LDL-C screening and not requiring uptitration with a fasting LDL-C at screening of ≥ 85 mg/dL (2.2 mmol/L). Enrollment of subjects with a screening fasting LDL-C between ≥ 85 mg/dL (2.2 mmol/L) and < 100 mg/dL (2.6 mmol/L) was limited to no more than approximately 20% of total planned enrollment.

Major exclusion criteria included the use of prescription lipid-regulating drugs other than statins or ezetimibe (eg, bile-acid sequestering resins, fibrates and derivatives), or the use ofstanols, red yeast rice, niacin (> 200 mg/day), or omega-3 fatty acid (> 1000 mg/day) (eg, DHA and EPA) in the last 6 weeks before the LDL-C screening assessment. 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 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. 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 (1.0 + 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

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, protein-free frozen liquid consisting of AMG 145 excipients. Placebo was administered at 1 of 2 regimens: Q2W SC at 2 mL per administration or Q4W SC at 6 mL per administration, injections were split as described above. The manufacturing batch numbers for placebo are provided in Listing 14-8.9.1.

Duration of Treatment: A maximum duration of 6 weeks was allowed for the screening and placebo run-in periods followed by a 12-week treatment period.

Study Endpoints:

Efficacy Endpoints:

The primary 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

- 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

Pharmacokinetics Endpoints

- serum concentration of AMG 145 and PCSK9 at selected time points
- time to maximal concentration (t_{max}), maximal concentration (C_{max}), minimum concentration (C_{min}), and area under the curve (AUC_t) 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 ($C_{min, LDL-C}$), the time at which the lowest LDL-C was observed ($T_{min, LDL-C}$), average LDL-C between weeks 8 to 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)

Exploratory efficacy endpoints are listed in Section 7.10.3.3.

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 3 AMG 145 doses administered Q2W compared with placebo, and (2) the treatment effects of 3 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 compared 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

Analyses of the secondary endpoints of change and percent change from baseline were similar to the primary analysis for the primary endpoint. No multiplicity adjustments were made for secondary and other non-primary endpoints.

Safety Analyses

Adverse events were coded by using Medical Dictionary for Regulatory Activities (MedDRA, version 15). Adverse events were summarized by treatment group assigned at randomization. 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 factors, 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 631 subjects were randomized. Overall, 474 subjects were randomized to 1 of the 6 AMG 145 groups (79 to 70 mg Q2W; 79 to 105 mg Q2W; 78 to 140 mg Q2W; 79 to 280 mg Q4W; 79 to 350 mg Q2W; 80 to 420 mg Q4W), 78 subjects were randomized to receive placebo Q2W, and 79 subjects were randomized to receive placebo Q4W. A total of 629 (99.7%) subjects received investigational product and were included in the full analysis set (FAS). A total of 630 subjects (99.8%) completed the study.

Baseline Demographics:

Sex: 50.7% women; 49.3% men

Age: mean (standard deviation) age was 60.5 (9.5) years

Ethnicity: 96.7% Not Hispanic or Latino; 3.3% Hispanic or Latino

Race: 88.7% white; 7.9% black; 1.9% Asian; 0.5% American Indian or Alaska native; 0.5% native Hawaiian or other Pacific Islander; 0.5% "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 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) with the exception of the 350 mg and 420 mg Q4W doses, which demonstrated similar reductions. Percent reductions in UC LDL-C relative to placebo (treatment difference) ranged from 42% (70 mg) to 66% (140 mg) in the Q2W groups and from 42% (280 mg) to 50% (350 mg and 420 mg) in the Q4W groups. Reductions in LDL-C occurred early in the treatment period (ie, at first observation at week 2) and were sustained through week 12 in all AMG 145 groups. Least-squares (LS) mean UC LDL-C percent reductions from baseline at week 12 ranged from 39% to 63% in the Q2W groups and from 43% to 51% in the Q4W groups, compared with a 3% increase in the Q2W placebo group and a 1% reduction in the Q4W placebo group.

Sensitivity analyses confirmed the primary efficacy analysis. Subgroup analyses (by stratification factors 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 the Q2W and Q4W dosing frequencies. Analyses adjusting for each of the baseline covariates in the primary analysis ANCOVA model showed results that were consistent with the primary analysis.

Analyses of secondary efficacy endpoints showed statistically significant ($p < 0.001$) reductions relative to placebo for all AMG 145 groups within the Q2W and Q4W dosing frequencies for each of the secondary efficacy endpoints (absolute change from baseline in 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 secondary efficacy endpoints, the reductions were dose-dependent within each AMG 145 dosing frequency (Q2W and Q4W) with the exception of the 350 mg and 420 mg Q4W doses, which demonstrated similar reductions.

Among the other parameters of efficacy (HDL-C, very low density lipoprotein cholesterol [VLDL-C], triglycerides, total cholesterol, ApoA1, and lipoprotein(a) [Lp(a)], PCSK9), treatment with AMG 145 resulted in statistically significant reductions ($p < 0.02$) relative to placebo at all AMG 145 doses and frequencies for percent change from baseline at week 12 in triglycerides, total cholesterol, VLDL-C, Lp(a), and for observed PCSK9 at week 12. Reductions in these parameters at week 12 were generally dose-dependent within the Q2W and Q4W dosing frequencies.

Treatment with AMG 145 also resulted in statistically significant increases ($p \leq 0.031$) in HDL-C relative to placebo at week 12 in all AMG 145 groups (except 280 mg Q4W). Statistically significant increases in ApoA1 relative to placebo were not observed at week 12 in any group except the 350 mg Q4W group ($p = 0.014$). Increases in HDL-C and ApoA1 were not dose-dependent in either (Q2W and Q4W) dosing frequency.

[redacted]

Pharmacokinetics Results: Serum AMG 145 concentrations increased with increasing dose and were accompanied by expected peak to trough changes over the dosing interval consistent with the frequency of administration. Pharmacokinetic data from the PK substudy indicated that PK 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 tmax occurred approximately 1 week following SC administration.

In the PK substudy, PCSK9 and calculated LDL-C pharmacodynamic parameters were estimated between weeks 8 and 12. The time-averaged reduction in PCSK9 as characterized by the area under the PCSK9 concentration time curve exhibited dose dependent increases in average PCSK9 lowering; the greatest reduction in PCSK9 occurred in the 140 mg SC Q2W and 420 mg SC Q4W groups. The Q2W regimens led to less maximal PCSK9 reduction than the Q4W dosing but also less return towards baseline. Time-averaged LDL-C parameters were estimated from calculated LDL-C values obtained during the PK substudy. The calculated LDL-C AUECweek8-12 generally exhibited dose-dependent lowering. The mean nadir of absolute calculated LDL-C (Cmin, LDL-C) in the PK substudy groups receiving AMG 145 doses ≥ 140 mg ranged from 19 mg/dL to 29 mg/dL indicating that AMG 145 administration to subjects receiving statins resulted in robust LDL-C lowering during the dosing interval.

Anti-AMG 145 Results: No subjects tested positive for anti-AMG 145 antibodies.

Safety Results: Overall, 348 (55.3%) subjects experienced at least 1 treatment emergent adverse event. The subject incidence of treatment emergent adverse events was higher in subjects receiving AMG 145 (58.4%, 277/474) than subjects receiving placebo (45.8%, 71/155). The most commonly reported treatment emergent adverse events in the AMG 145 group (AMG 145, placebo) were nasopharyngitis (10.1%, 7.1%), cough (3.4%, 1.9%), and nausea (3.2%, 0.6%). No relationship between the subject incidence of treatment emergent adverse events and the AMG 145 dose or dosing frequency was observed. Treatment related adverse events were reported for 8.2% (39/474) of subjects receiving AMG 145 and 7.1% (11/155) of subjects receiving placebo. The most commonly reported treatment related adverse events in the AMG 145 group (> 2 subjects) (AMG 145, placebo) were muscle spasms (0.8%, 1.3%), diarrhea (0.8%, 0.6%), nausea (0.6%, 0%), and flushing (0.6%, 0%).

The subject incidence of CTCAE grade 3 adverse events was similar between the AMG 145 (13/474 [2.7%]) and placebo (4/155 [2.6%]) groups. All grade 3 adverse events were single occurrences except diarrhea, which occurred in 1 subject each in the AMG 145 140 mg Q2W group and the placebo Q4W group. One (0.2%) subject in the AMG 145 group and no subjects in the placebo group had a grade 4 adverse event (acetabulum fracture in AMG 145 140 mg Q2W).

There was one on-study death (described in the efficacy summary).

The subject incidence of serious treatment emergent adverse events was similar between the AMG 145 (2.3%, 11 subjects) and placebo groups (2.6%, 4 subjects). One event of coronary artery bypass [redacted] was inadvertently included as a serious adverse event in the final clinical database and resulting tables and listings (refer to Appendix 21, Database Errata). Serious treatment emergent adverse events of cellulitis and pneumonia were each reported in 2 (0.3%) subjects; each event occurred in 1 subject in the AMG 145 140 mg Q2W group and 1 subject in the AMG 145 350 mg Q4W group. All other serious adverse events were single occurrences.

Two (0.4%) subjects in the AMG 145 group (140 mg Q2W) and no subjects in the placebo group experienced adverse events leading to discontinuation of investigational product.

No risk was identified from the evaluation of the events of interest. [redacted] No trends indicative of clinically important adverse effects of AMG 145 were observed on selected laboratory variables, ECGs, or vital signs during the study.

Conclusions: Treatment with AMG 145 in combination with statin therapy resulted in statistically significant 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 from baseline relative to placebo at week 12 for the 140 mg Q2W and 420 mg Q4W dose groups were 66% and 50%, respectively.

Treatment with AMG 145 in combination with statin therapy also resulted in statistically significant reductions relative to placebo for all AMG 145 groups within the Q2W and QW4 dosing frequencies for each 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) ($p < 0.001$). Percent reductions for the primary endpoint and the secondary endpoints were dose-dependent within each AMG 145 dosing frequency (Q2W and Q4W) with the exception of the 350 mg and 420 mg Q4W doses, which demonstrated similar reductions.

Results from the PK substudy indicated that AMG 145 exposure increased with increasing dose and was approximately linear for SC doses ≥ 140 mg. The time-averaged reduction in PCSK9 as characterized by the area under the PCSK9 concentration time curve exhibited dose dependent increases in average PCSK9 lowering; the greatest reduction in PCSK9 occurred in the 140 mg SC Q2W and 420 mg SC Q4W groups. Dose dependent reductions in the calculated LDL-C $AUEC_{week8-12}$ were generally observed and consistent with the lowering in PCSK9. The mean nadir of absolute calculated LDL-C ($C_{min, LDL-C}$) in the PK substudy groups receiving AMG 145 doses ≥ 140 mg indicated that AMG 145 administration to subjects receiving statins resulted in robust LDL-C lowering during the dosing interval.

Treatment with AMG 145 in this setting did not result in clinically significant safety findings. The overall subject incidence of treatment emergent adverse events was higher in AMG 145 groups compared with placebo. No relationship was observed between the subject incidence of treatment emergent adverse events and the AMG 145 dose or dosing frequency.

[redacted]