2 SYNOPSIS

Name of Sponsor: CSL Behring, LLC	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: CSL112		
Name of Active Ingredient: Apolipoprotein A-I (apoA-I) [human]		

Title of Study:
A Phase 2, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group, Study to Investigate the Safety and Tolerability of Multiple Dose Administration of CSL112 in Subjects with Moderate Renal Impairment and Acute Myocardial Infarction

Coordinating Investigator: PPD, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 USA

Publication (reference): None

Study Period: *First Subject Visit*: 12 August 2016 *Last Subject Visit*: 28 June 2017	**Phase of Development:** 2

Objectives:

Primary Objective: To assess the renal safety of CSL112 in subjects with moderate renal impairment (RI) and acute myocardial infarction (AMI) after administration of up to 4 weekly infusions of CSL112.

Secondary Objectives:

1. To further characterize the safety and tolerability of CSL112 in subjects with moderate RI and AMI.
2. To characterize the pharmacokinetics (PK) of CSL112 after multiple dose administration in subjects with moderate RI and AMI.

Exploratory Objectives:

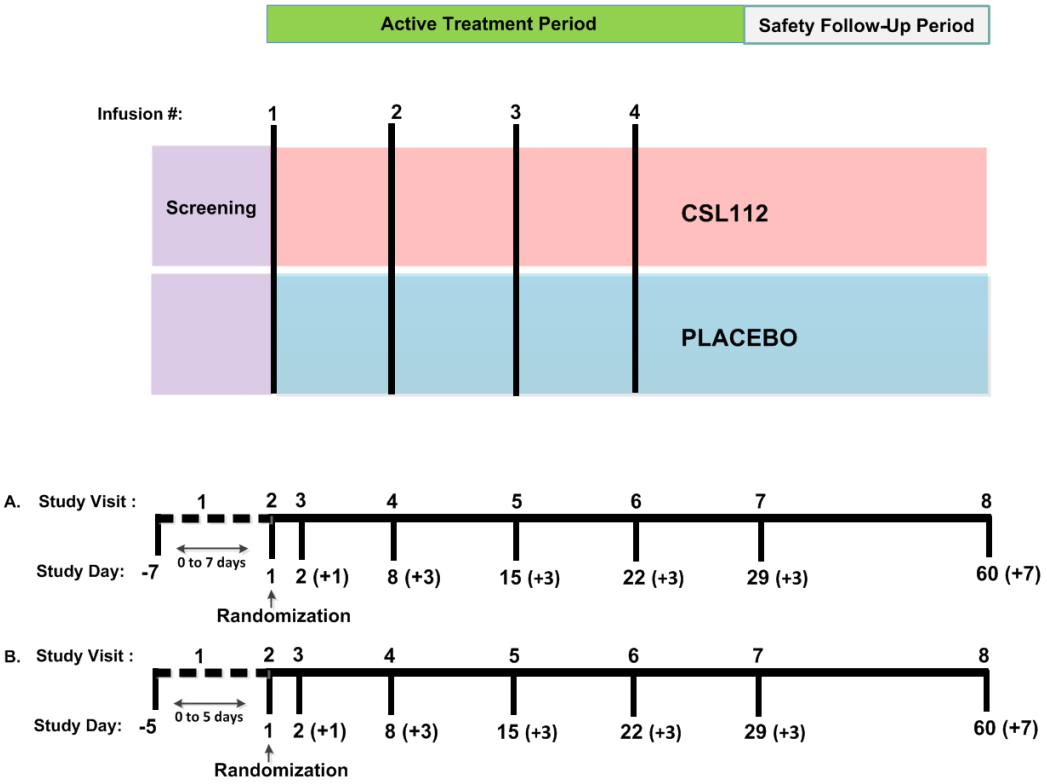
1. To characterize the pharmacodynamic (PD) features of CSL112 by evaluating cholesterol efflux and other lipid and cardiovascular (CV) biomarkers of CSL112 activity.
2. To assess the effect of CSL112 on renal safety biomarkers.

Methodology:

This was a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and tolerability of up to 4 weekly intravenous (IV) administrations of 6 g CSL112 compared with placebo in subjects with moderate RI and AMI. The study was conducted at 37 centers globally in the United States (US), Germany,

Hungary, Israel, and the Netherlands. The study consisted of a Screening Period and 2 study periods: an Active Treatment Period during which patients received up to 4 IV infusions of investigational product (ie, CSL112 6 g or placebo), a minimum of 7 days apart, over approximately 29 days and a Safety Follow-up Period (approximately 30 days from end of the Active Treatment Period) (depicted below).

Overview of Study Design



AMI = acute myocardial infarction; DSMB = Data and Safety Monitoring Board; IV = intravenous; FMC = first medical contact

A) In the United States, prior to the 13 February 2017 DSMB recommendation to allow earlier dosing, subjects were assessed for eligibility during screening and up to and including randomization (Visit 1 and Visit 2 before infusion), which occurred no later than 7 days after FMC for the index AMI.

B) From study start in countries outside of the United States and after the 13 February 2017 DSMB recommendation, the Screening Period up to and including randomization had to occur within 5 days of FMC for the index AMI.

Subjects were screened and after provision of written informed consent were randomly assignment in a 2:1 ratio to receive infusions of 6 g CSL112 (54 subjects) versus placebo (27 subjects) to evaluate safety. To ensure that at least one-third of the study population had an estimated glomerular filtration rate (eGFR) in the chronic kidney disease (CKD) stage 3b range (eGFR 30 to < 45 mL/min/1.73 m^2), no more than two-thirds of the study population (ie, 54 subjects) were to have an eGFR in the CKD 3a range (45 to < 60 mL/min/1.73 m^2). Randomization was stratified by eGFR (30 to < 45 mL/min/1.73 m^2 or 45 to <60 mL/min/1.73 m^2) as calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI)

equation, and by medical history of diabetes requiring current treatment with any anti-diabetic medication (yes or no).

A subset of up to 21 enrolled subjects were planned for participation in a PD substudy, which was intended to characterize the profile of biomarkers of inflammation in response to an ex-vivo inflammatory stimulus in whole blood after CSL112 6 g administration. Results of the PD substudy will be reported separately.

Number of Subjects:
Planned: 81 subjects
Actual: 83 subjects

Diagnosis and Main Criteria for Inclusion:

Males or females aged at least 18 years at the time of providing written informed consent with evidence of moderate RI (eGFR ≥ 30 and < 60 mL/min/1.73 m^2) before randomization, as calculated by the interactive response technology using the CKD-EPI equation, and evidence of myocardial necrosis in a clinical setting consistent with a type I (spontaneous) AMI.

Investigational Product, Dose and Mode of Administration, Batch Number(s):

Investigational product (6 g CSL112 or placebo [0.9% saline]) was administered once weekly as a 2-hour IV infusion into a suitable peripheral or central vein.

Duration of Treatment:

For an individual subject, the maximum study duration was approximately 9 weeks from Screening to final visit. This duration was based on a 5-day Screening Period, a 4-week Active Treatment Period and a 4-week Safety Follow-up.

Criteria for Evaluation:
Co-primary Endpoints:

1. Incidences of treatment-emergent renal serious adverse events (SAEs).
2. Acute kidney injury (AKI), defined as an absolute increase in serum creatinine from baseline ≥ 0.3 mg/dL (≥ 26.5 µmol/L) during the Active Treatment Period that was sustained upon repeat measurement by the central laboratory no earlier than 24 hours after the elevated value. If no repeat value was obtained (due, for example, to loss of follow-up or protocol violation), a single serum creatinine value that was increased from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period also fulfilled the definition of AKI. Baseline for determination of AKI was defined as the

pre-infusion central laboratory serum creatinine level on Study Day 1.

Secondary Endpoints:
Safety

1. The occurrence of any treatment-emergent adverse events (TEAEs) throughout the study.
2. The occurrence of treatment-emergent adverse drug reactions or suspected adverse drug reactions.
3. Changes from baseline (ie, pre-infusion on Study Day 1) through to the end of the Active Treatment Period in renal status.
4. Change from baseline (ie, pre-infusion on Study Day 1) in hepatic status that occurred during the Active Treatment Period and that was sustained for ≥ 24 hours upon repeat measurement.
5. The occurrence of treatment-emergent bleeding events as defined by the Bleeding Academic Research Consortium (BARC) criteria from the start of the first infusion until the end of the Safety Follow-up Period.
6. Clinically significant changes in clinical laboratory tests results (serum biochemistry, hematology, and urinalysis), physical examinations findings, body weight, electrocardiograms (ECGs), and vital signs (blood pressure, pulse rate, and body temperature).
7. The occurrence of binding antibodies specific to apoA-I and/or CSL112.

Pharmacokinetic

1. Baseline (ie, pre-infusion on Study Day 1)-corrected plasma apoA-I concentrations.
2. Baseline-corrected plasma phosphatidylcholine (PC) concentrations.
3. Concentration in plasma at End-of-Infusion for apoA-I and PC.
4. Accumulation ratio (RA) for apoA-I and PC.

Exploratory Endpoints

1. Change from baseline in lipid/lipoprotein and CV biomarkers as measured throughout the course of treatment.
2. Change from baseline in renal safety biomarkers.

Lipid/lipoprotein biomarkers included: Ex-vivo cholesterol efflux measures, apolipoprotein B, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein

cholesterol (LDL-C), non HDL-C, and triglycerides.

CV biomarkers included: High sensitivity cardiac troponin I, high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), and N-terminal pro-brain natriuretic peptide (NT proBNP).

Renal safety biomarkers included: serum cystatin C, urine cystatin C / creatinine ratio, urine protein / creatinine ratio, and urine albumin / creatinine ratio.

Statistical Methods:
No statistical hypothesis testing was performed in this study.

Determination of Sample Size: The planned sample size for this study was 81 subjects, with 54 to receive active treatment and 27 to receive placebo. The cohort size was chosen such that the study would detect with 80% probability a treatment-emergent event with a frequency of 3% in the active group and 2% overall. It was planned to meet regulatory considerations for treatment-emergent renal event characterization; it was not powered for statistical testing of the co-primary endpoints.

Analysis Populations: The study had 6 analysis populations. The All Subjects Screened (SCR) Population consisted of all subjects who provided written informed consent to undergo study screening procedures. The Intent-to-Treat (ITT) Population consisted of all subjects in the SCR Population who were randomized to 1 of the 2 treatment groups. The Safety (SAF) Population consisted of all subjects in the ITT Population who received at least a partial dose of investigational product. The PK Population consisted of all subjects in the SAF Population who had at least 1 measurable plasma concentration of apoA-I or PC. The Biomarker (BM) Population consisted of all subjects in the SAF Population who had at least 1 measurable concentration (or activity) of exploratory biomarkers. The PD substudy population was a subset of subjects from the SAF population who consented to participate in the PD substudy.

Pharmacokinetic Methods: Measured (uncorrected) plasma concentrations and baseline-corrected (change from baseline) concentrations of apoA-I and PC were listed and summarized by time point, by treatment, and by renal function stratum for the PK population. A summary table for maximal concentration in plasma (C_{max}) and RA was produced. Both measured and baseline-corrected maximum concentrations at the end of infusion 1 and the end of infusion 4 were provided. The RA was derived as the ratio of baseline-corrected End of Infusion 4 / baseline-corrected End of Infusion 1.

Pharmacodynamic Methods: Cardiovascular biomarkers were listed and summarized for the BM population overall and by renal function stratum (based on the eGFR [Central

Laboratory] values), for measured values, including baseline. Descriptive statistics included the geometric mean, geometric SD and the coefficient of variation, in addition to the number of subjects in the analysis (n), the mean, SD, median, minimum, and maximum. Baseline and change from baseline for lipid (ie, ex vivo cholesterol efflux capacity and other lipids/lipoproteins) and renal (serum cystatin C) biomarkers as measured throughout the course of treatment (ie, by visit) were summarized for the BM population overall and by renal function stratum (based on the eGFR [Central Laboratory] values).

Co-primary Endpoint Analyses: Analysis of the co-primary endpoints was conducted at study completion (when all randomized subjects either completed Visit 8/Study Day 60, had withdrawn from the study, or had been lost to follow-up) or after the study was terminated early based on recommendation of the independent DSMB and endorsement by the Steering Committee. For each co-primary endpoint, a Newcombe-Wilson two-sided 95% confidence interval around the difference in incidence rates was calculated if at least 1 event occurred. Otherwise, an exact, one-sided, upper 97.5% confidence interval was reported for the incidence rate in each treatment arm. Multiple sensitivity analyses were conducted. Subgroup analyses were performed based on eGFR and diabetes mellitus status.

Safety Analyses: An overview summary of TEAEs was produced, including counts and percentages of subjects as well as the number of events, across all preferred terms (PTs) for key categories of TEAEs and serious TEAEs. Adverse events (AEs) associated with bleeding events, hemolysis, and drug hypersensitivity reactions were considered AEs of special interest and were summarized. Summaries were provided based on the number and percentage of subjects experiencing each unique PT for fatal TEAEs and study treatment-related treatment-emergent fatal SAEs. Treatment-emergent AEs leading to permanent discontinuation of study treatment, withdrawal from the study, infusion interruptions, infusion delays, and skipped infusions were summarized by PT based on the number and percentage of subjects experiencing each unique PT. Individual subject data was provided in listings.

Central laboratory data were summarized with descriptive statistics, by treatment group and scheduled visit for the serum biochemistry, hematology and urinalysis parameters. Summaries of actual vital sign measurements (systolic and diastolic blood pressure, pulse, temperature, and weight), changes from baseline by visit, and shifts from baseline according to markedly abnormal criteria were provided.

The ECG parameter actual values and changes from baseline were summarized descriptively by visit. Incidence of treatment emergent markedly abnormal ECG intervals was summarized. The number and percentage for each ECG investigator-assessed category at

baseline and the shift from baseline to the last assessment in the Active Treatment Period was reported.

Any abnormal physical examination findings considered by the Investigator as clinically significant at the time of screening were documented as medical history. Any clinically significant changes which occurred between screening and the end of the study, including drug hypersensitivity findings were documented as an AE.

Immune response to investigational product was evaluated based on frequencies and percentages of subjects at baseline, Visit 7, and Visit 8. Data were summarized by treatment group and a by-subject listing was produced.

Individual subject data was provided in listings.

Results:

Subject Disposition

A total of 102 subjects provided written informed consent and were screened for inclusion in the study. The percentage of subjects with Stage 3a CKD and a medical history with diabetes requiring treatment with any anti-diabetic medication (16.9%) was approximately half that of subjects with Stage 3a CKD and a medical history without diabetes requiring treatment with any anti-diabetic medication (36.1%); whereas, the percentage of subjects with Stage 3b CKD and a medical history with (25.3%) or without (21.7%) diabetes requiring current treatment with any anti-diabetic medication was relatively similar. Within each of the 4 possible stratification categories, the percentage of subjects in each treatment group was similar. Of the subjects who were screened, 19 were screen failures, and the remaining 83 (81.4%) eligible subjects were randomized 2:1 active to placebo to receive 6 g of CSL112 (55 subjects, 53.9%) or placebo (28 subjects, 27.5%), respectively. Sixty-nine (83.1%) randomized subjects completed the study, with 46 / 55 (83.6%) subjects completing in the CSL112 6 g group and 23 / 28 (82.1%) subjects completing in the placebo group.

Demographics and Baseline Characteristics

Subjects were predominantly white (96.4%), not Hispanic or Latino (95.2%), and male (66.3%). Geographically, 22.9% of subjects were from the US, and 33.7% and 43.4% were from Eastern and Western European-like countries, respectively. The subject mean age was 71.1 years, with 81.9% of subjects at least age 65 years, and with a mean BMI of 29.5 kg/m^2. Most subjects (73.5%) had their index myocardial infarction (MI) event classified as non ST-segment elevation myocardial infarction (NSTEMI). Overall, 48.2% percentage of subjects had a medical history of diabetes, with 42.2% requiring current treatment with any

anti-diabetic medication. Subjects were receiving aspirin (95.2%), other anti-platelet drugs (91.6%), statins (89.2% overall; 59.0% high intensity), other lipid modifying agents (6.0%), beta-blockers (79.5%), angiotensin I converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) [74.7%], oral anti-thrombotics (ie, other anti-coagulants, 26.5%), and other lipid modifying agents (6.0%). In general, use of medications of interest at baseline was comparable between treatment groups, although there was higher baseline use of ACE-I/ARBs in subjects randomized to CSL112 6 g (80.0%) compared with placebo (64.3%).

Pharmacokinetics

- Increases in apoA-I and PC plasma concentrations were observed after CSL112 6 g infusion relative to baseline and to placebo overall and for each renal function strata.
- There was low plasma accumulation of apoA-I or PC with CSL112 6 g treatment in subjects with AMI and moderate RI. Mean (SD) accumulation ratios at peak were 1.2 (0.32) for apoA-I and 1.0 (0.36) for PC with CSL112 6 g treatment.

Pharmacodynamics

- At baseline, there was no difference between CKD 3a and 3b strata in cholesterol efflux capacity (total, adenosine triphosphate -binding cassette transporter protein subfamily A member 1 [ABCA1]-independent, and ABCA1-dependent).
- Increases in cholesterol efflux capacity (total, ABCA1-independent, and ABCA1-dependent) were observed after CSL112 6 g infusion relative to baseline overall and for each renal function strata. No increase in cholesterol efflux capacity relative to baseline was observed with placebo infusion.
- At baseline, there was no difference observed between CKD 3a and 3b strata in levels of total cholesterol, HDL-C, non HDL-C, LDL-C, and apoB. Numerical differences were noted in baseline mean values for triglycerides between renal function strata; however, these differences were not significant.
- During the Active Treatment Period, HDL-C was increased relative to baseline in the CSL112 6 g group with no change observed in the placebo group.
- No changes in atherogenic lipoproteins (LDL-C, apoB, total cholesterol) or triglycerides were observed with CSL112 6 g infusion compared with placebo.
- At baseline, geometric mean values of hsCRP, hsTroponin I, IL-6, and NT proBNP were higher in the CKD 3b strata compared with the CKD 3a strata, with statistically

significant differences observed for IL-6 and NT proBNP.

- Decreases in mean concentrations of all CV biomarkers (hsCRP, hsTroponin I, IL-6, NT proBNP) were observed at the end of the Active Treatment Period compared with baseline with little difference observed between treatment groups.

Safety

The following conclusions can be made based on the safety evaluation:

- Most (81.3%) subjects received 3 or 4 infusions of CSL112 6 g or placebo; the most frequent reason for not completing all 4 infusions was TEAEs.

Co-primary Endpoints

- Results did not provide evidence for an increased risk of renal SAEs or AKI events in subjects treated with CSL112 6 g versus placebo.

Other Renal Safety Endpoints

- There was no evidence of a higher rate of creatinine elevations with CSL112 6 g compared with placebo by either central or local laboratory analysis.
- No subjects in the CSL112 6 g or placebo group experienced a Stage 3 AKI event.

Hepatic Findings

- There were no potential Hy's Law cases as defined by concomitant elevations in ALT to > 3 × ULN and total bilirubin to > 2 × ULN for subjects in either treatment group.
- Mild, transient increases in total bilirubin >1.5x ULN (or direct bilirubin for subjects with Gilbert's syndrome) were observed in the 24 to 48 hours after the start of infusion 1 in a small percentage (3 / 52, 5.8%) of subjects who received CSL112 6 g and no subjects in the placebo group.

Treatment-emergent AEs

- There was a similar frequency of TEAEs in the CSL112 6 g (38 / 52, 73.1%) and placebo (20 / 28, 71.4%) groups.
- Treatment-emergent AEs reported for 5% or more subjects in the CSL112 6 g group alone included Blood creatinine increased, Cardiac failure, and Atrial fibrillation. For the placebo group alone these included Noncardiac chest pain, Hypotension, and Cough.

- A lower percentage of SAEs were reported in the CSL112 6 g group (12 / 52, 23.1%) compared with the placebo group (10 / 28, 35.7%).
- Treatment-emergent AEs leading to permanent discontinuation of investigational product or skipped infusions were more prevalent in the CSL112 6 g group (21.2%) compared with the placebo group (14.3%). One subject in the CSL112 6 g group (1.9%) withdrew from the study due to AEs.
- A higher percentage of subjects in the CSL112 6 g group (7 / 52, 13.5%) compared with the placebo group (2 / 28, 7.1%) had TEAEs of heart failure; however, treatment-emergent SAEs of heart failure occurred at a similar frequency in both treatment groups (CSL112 7.7% vs placebo 7.1%).
- Two deaths occurred in each treatment group; no deaths were assessed as related to investigational product.
- No AEs related to hemolysis were identified and the incidence of bleeding events was low, with no difference between treatment groups. There were no BARC Grade 4 / 5 bleeding events.
- One drug hypersensitivity event was reported for 1 (1 / 52, 1.9%) subject in the CSL112 6 g group. The event was not serious and was considered to be not related to investigational product.

<u>Clinical Laboratory and Other Safety Evaluations</u>

- A small, transient increase in the mean (but not median) urine cystatin C/creatinine ratio was observed in the CSL112 6 g group at 24 to 48 hours after the start of infusion 1, but with large variability. There was no treatment effect on total protein / creatinine or albumin / creatinine ratios.
- Serum cystatin C levels were similar between treatment groups.
- No antibodies to CSL112 or apoA-I were detected in either treatment group.
- There were no clinically meaningful differences between treatment groups in vital sign or ECG parameters.

Conclusions:

CSL112 at a dose of 6 g administered between 12 hours and 5 days after an AMI as 4 weekly infusions in subjects with moderate RI receiving standard of care therapy was well tolerated and demonstrated acceptable renal safety. Infusion of CSL112 caused an increase in apoA-I with low accumulation, confirming the appropriateness of the 6 g dose in subjects with moderate RI. Likewise, there was an increase in cholesterol efflux capacity, confirming the mechanism of action in this population, and consistent with prior studies. Based on these findings, inclusion of subjects with AMI and moderate RI is appropriate for further assessment of the clinical efficacy of CSL112 for reducing recurrent CV events in an adequately powered Phase 3 trial.

Date of Report: 18 December 2017