2 SYNOPSIS

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

Title of Study:
A Phase 2b, Multi-center, Randomized, Placebo-controlled, Dose-ranging Study to Investigate the Safety and Tolerability of Multiple Dose Administration of CSL112 in Subjects with Acute Myocardial Infarction (AEGIS-I)

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Publication (reference):
Gibson MC, Korjian S, Tricoci P, Daaboul Y, Yee M, Jain P, et al. Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Apolipoprotein A-I, After Acute Myocardial Infarction: The AEGIS-I Trial (ApoA-I Event Reducing in Ischemic Syndromes I). Circulation. 2016 Dec 13;134(24):1918-1930.

Study Period: *First Subject Visit*: 15 August 2014 *Last Subject Visit*: 07 March 2016	**Phase of Development:** Phase 2b

Objectives:

***Primary Objective*:** The primary objective of this study was to assess the hepatic and renal safety and tolerability of multiple dose administration of 2 dose levels (low dose [2 g] or high dose [6 g]) of CSL112 compared with placebo in subjects with acute myocardial infarction (AMI).

***Secondary Objectives*:** Secondary objectives of the study were to examine the effect of CSL112 on the time-to-first occurrence of major adverse cardiovascular events (MACE), as adjudicated by the Clinical Events Committee (CEC); to characterize the safety and tolerability of CSL112; and to characterize the pharmacokinetics (PK) of CSL112 after multiple dose administration.

***Exploratory Objectives*:** The exploratory objectives of the study were further characterization of safety and tolerability; characterization of the PK and pharmacodynamic (PD) features of CSL112 in subjects with AMI; evaluation of the effect of CSL112 on the individual components of the 2°MACE composite, additional MACE composites, and additional MACE components; and evaluation of the relationship between healthcare resource utilization and treatment with CSL112.

Methodology:

This was a phase 2b, multi-center, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to investigate the hepatic and renal safety and tolerability of multiple dose administration of 2 dose levels of CSL112 (low dose [2 g] or high dose [6 g]) compared with placebo in subjects with AMI and either normal renal function or mild renal impairment who were receiving standard of care therapy. The study consisted of a safety lead-in period, the main study, a PK/PD substudy, and a MACE follow-up period.

Men and women, at least 18 years of age, with a clinical presentation consistent with a type I (spontaneous) myocardial infarction (MI) and who had either normal renal function (estimated glomerular filtration rate [eGFR] $\geq$ 90 mL/minute/1.73 m^2) or mild renal impairment (eGFR < 90 mL/minute/1.73 m^2 and $\geq$ 60 mL/minute/1.73 m^2) were to be enrolled. All subjects were required to have documented evidence of stable renal function at least 12 hours after the index event and before receiving the first dose of investigational product (IP).

The safety lead-in was designed to provide an early assessment of the safety profile of CSL112 before initiating the main study. The first 8 eligible subjects were to be evenly stratified by renal function and randomly assigned (3 active: 1 placebo) to receive a single 2 g dose of CSL112 (6 subjects) or placebo (2 subjects). The safety lead-in period was to continue until at least 8 subjects, including 4 subjects with mild renal impairment, received a single 2 g dose of CSL112 or placebo and completed a 7-day safety follow-up visit.

Study enrollment was to be paused after completion of the safety lead-in in order for the Data and Safety Monitoring Board (DSMB) to review the data from the safety lead-in before making a recommendation as to whether or not the main study may proceed as designed. Following recommendation from the DSMB, enrollment into the main study was to proceed. Approximately 1200 subjects were to be randomly assigned to 1 of 3 treatment groups (2 g CSL112, 6 g CSL112, or placebo; 400 subjects per group). Subjects were to receive four, 2-hour infusions of IP (CSL112 or placebo), a minimum of 7 days apart, during the 4-week active treatment period.

Study assessments for all subjects in the main study (including those in the PK/PD substudy) were to be conducted at screening, before and after infusions during the 4-week active treatment period, at the end of the active treatment period (Visit 6/Study Day 29), 60 days after first infusion for adverse event (AE) assessment, and at approximately 90 days after last administration of IP. Subjects were to be followed for the occurrence of MACE at approximately 90-day intervals thereafter until the last subject treated completed Visit 8/Study Day 112.

A subset of 48 subjects was planned for an optional PK/PD substudy, which was designed to characterize the PK/PD profile of CSL112 when administered as a multiple dose

regimen. Additional blood samples were to be collected from subjects in the PK/PD substudy for purposes of the PK and PD analyses. Subjects were to be screened and eligible subjects equally stratified by renal function group and randomly assigned (3:3:2 [2 g: 6 g: placebo]) to 1 of 3 treatment groups (18:18:12 [2 g: 6 g: placebo]).

Number of Subjects:

***Planned*:** Approximately 1208 subjects were planned for enrollment, including a minimum of 8 subjects in the safety lead-in period and 1200 subjects in the main study (including approximately 48 subjects in the PK/PD substudy)

***Actual*:** A total of 1267 subjects were enrolled and randomized (9 subjects in the lead-in and 1258 subjects in the main study). A total of 1253 subjects were treated and analyzed for safety (9 subjects in the lead-in and 1244 in the main study [including 63 in the PK/PD substudy])

Diagnosis and Main Criteria for Inclusion:

Men or women at least 18 years of age with evidence of myocardial necrosis in a clinical setting consistent with a type I (spontaneous) AMI as defined by the following:

1. Detection of a rise and/or fall cardiac troponin I or T with at least one value above the 99th percentile upper reference limit.

AND,

2. Any one or more of the following:
    a. Symptoms of ischemia
    b. New (or presumably new) significant ST/T wave changes or left bundle-branch block (LBBB)
    c. Development of pathological Q waves on electrocardiogram (ECG)
    d. Imaging evidence of new loss of viable myocardium or regional wall motion abnormality
    e. Identification of intracoronary thrombus by angiography

Evidence of stable renal function at least 12 hours after the index event. In addition, for subjects who underwent angiography and, therefore, had received intravenous (IV) contrast agent, stable renal function was defined as an increase in serum creatinine obtained at least 12 hours after contrast administration that was < 0.3 mg/dL from the pre-contrast administration value. If the local laboratory post-contrast serum creatinine value was ≥ 0.3 mg/dL from the pre-contrast administration value, the laboratory test may have been repeated once at least 24 hours after the initial assessment to determine eligibility and stable renal function. The repeat serum creatinine value must have been < 0.3 mg/dL from the pre-contrast administration value. Only subjects with repeat serum creatinine values < 0.3 mg/dL from the pre contrast administration value were eligible, provided no suspicion of acute kidney injury existed.

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

The IP was CSL112, and the comparator was placebo. CSL112 resembles nascent high-density lipoprotein (HDL) and contains disc-shaped, noncovalently associated particles formed from apoA-I and phosphatidylcholine (PC); other components include sodium cholate and sucrose. CSL112 was supplied as a sterile and lyophilized powder in a 100 mL glass bottle with a rubber stopper and an aluminum cap. CSL112 was reconstituted with 50 mL of Water for Injection (WFI), yielding approximately 57 mL of product ready-for-use and was administered as a nominal dose of 2 g (1 vial) or 6 g (3 vials). The placebo comparator was sterile, colorless 0.9% sterile saline, which was administered in a volume matched to either the 2-g or 6-g CSL112 infusion volume.

CSL112 and placebo were administered by a 2-hour IV infusion into a suitable vein (peripheral or central).

The batch numbers of CSL112 used in this study were 4376000001, 4376000002, 4376000003, 4376000004, 4376000005, 4376000006, 4376000007, 4376000008, 4376000009, 4376000010, 4376000012, 4376000013, 4376000014, 4376000015, 4376000016, 4376000017, 4376000018, 4376000019, 4376000020, and 4376000021. The batch numbers of placebo used in this study were 14C19G62, 14C19G62, 14G26G62, 46-073-JT-01, and 39-009-JT-02.

Duration of Treatment:

Safety lead-in period:

The minimum duration of an individual subject in the safety lead-in period was expected to be approximately 9 days (including screening), with a maximum of approximately 91 days.

Main study:

The minimum duration of the main study for an individual subject was expected to be approximately 112 days (16 weeks). The maximum duration for an individual subject was expected to be approximately 382 days (57 weeks). This estimation was based on a 7-day screening period, a 4-week treatment period, and a minimum 12-week/maximum 52-week MACE Follow-up Period.

Overall Study Duration:

The overall duration (ie, first subject's screening visit [safety lead-in] to last subject's end of study visit [main study]) was approximately 19 months.

Criteria for Evaluation:

***Co-Primary Endpoints*:** Hepatic and renal safety and tolerability were assessed by the following two outcome measures:

- A clinically important change from baseline through to the end of the treatment period (V6/Study Day 29) in biomarkers of drug-induced liver injury (DILI) that were confirmed upon repeat measurement by the central laboratory. A clinically important change was defined as:
  - Alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN), OR
  - Total bilirubin > 2 x ULN
- A clinically important change from baseline through to the end of the treatment period (Visit 6/Study Day 29) in renal status was defined as:
  - Serum creatinine increase to ≥ 1.5 x the baseline value (Kidney Disease Improving Global Outcomes, March 2012)that is confirmed as determined upon repeat measurement by the central laboratory or the need for renal replacement therapy

***Secondary Endpoints*:** Secondary endpoints included time-to-first MACE (cardiovascular [CV] death, nonfatal MI, ischemic stroke, hospitalization for unstable angina), safety and tolerability endpoints (adverse drug reactions or suspected adverse drug reactions, all AEs, bleeding events as defined by the Bleeding Academic Research Consortium [BARC] criteria), immunogenic potential of CSL112, and serology and nucleic acid testing (NAT) for presence of parvovirus B19), and PK parameters (baseline-corrected plasma apoA-I concentrations, PC concentrations, and noncompartmental parameters).

Exploratory Endpoints: Exploratory endpoints included additional safety and tolerability assessments, exploratory PD endpoints (including CV biomarkers and cholesterol efflux measures), exploratory MACE composites and components, and a population PK analysis (to be reported separately).

Statistical Methods:

Data for the safety lead-in period were summarized and listed separately from data for the main study; all summaries for the safety lead-in period were descriptive only.

Efficacy analyses

The efficacy endpoints for this study were either secondary or exploratory in nature. For the composite MACE endpoints (secondary and exploratory), the time-to-first MACE was analyzed using a Cox proportional hazards model, with covariates of treatment and baseline renal function stratum. The number of subjects with events, the hazard ratio and 95% confidence interval, the one-sided Wald p-value for the hazard ratio, and the stratified log rank test p-values for the comparison of the time-to-first MACE for each CSL112 dose group to placebo were reported. Plots based on the 1 minus Kaplan-Meier (1-KM) method were produced for all treatment groups, and Forest plots displaying the hazard ratios and number of subjects with MACE in each treatment group were produced.

Pharmacokinetic Analysis

The PK/PD population (only subjects who participated in the PK/PD substudy) was used for

the noncompartmental PK analysis. The parameters were calculated for both measured and baseline-corrected apoA-I and PC plasma concentrations, wherever possible, using WinNonLin® Version 6.3 (Phoenix Build 6.3.0.395) from concentration/activity-time data following the first and fourth infusions of placebo and CSL112 (2 g and 6 g); these data were summarized overall (by treatment group) and by renal function.

Pharmacodynamic Analysis

Observed (uncorrected), baseline-corrected, and infusion 4 pre-dose corrected values were summarized descriptively by visit for each of the cardiovascular, lipid, metabolic, and renal biomarkers (unless otherwise specified). Of note, renal biomarkers from blood (cystatin C) and urine (kidney injury molecule-1 and creatinine) samples were reported only for the PK/PD substudy.

Safety Analysis

Analyses were performed to test the non-inferiority of CSL112 to placebo for both co-primary endpoints. The co-primary analyses were conducted jointly with an overall significance level of 5%. All other p-values were considered exploratory. Confidence intervals were 95%, and all exploratory testing was two-sided, unless otherwise specified in the description of the analyses.

For the co-primary hepatic and renal safety endpoints assessed for each subject, the Bonferroni method was used to control the overall Type I error at 5%, giving 2.5% Type I error to each of the hepatic and renal endpoints. However, multiplicity adjustment was not applied to the two pairwise treatment group comparisons within each co-primary endpoint. The Newcombe-Wilson score method was used to calculate the two-sided 95% confidence intervals of the difference (CSL112 - Placebo) in rates. The upper bound of the 95% confidence interval was used for testing, which was equivalent to a 2.5% one-sided confidence test of the rate difference. The margins of non-inferiority, based on historical data, were chosen as 4% and 5% for the hepatic and renal endpoints, respectively.

For secondary safety endpoints, categorical elevations in laboratory abnormalities were summarized for ALT and serum creatinine. For all serum chemistry and laboratory results, actual values and changes from baseline to each visit were summarized descriptively by treatment group and scheduled visit, and shifts from baseline to worst observation in the active treatment period were also summarized. Grade 3 and 4 (ie, predefined clinically significant) laboratory abnormalities were also summarized by timepoint and overall.

Treatment-emergent adverse events (TEAEs) were defined as AEs that occurred after the start of the first infusion. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 19.0, and TEAEs were summarized by system organ class (SOC) and preferred term (PT). Summaries were provided for any TEAE, serious TEAE, TEAE with Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3, study-drug-related TEAE, TEAE of special interest (ie, bleeding events, hemolysis events, and drug hypersensitivity reactions), suspected adverse drug reaction as defined by the United States Food and Drug Administration (FDA), TEAE with outcome of death, TEAE leading to permanent discontinuation of IP.

Urinalysis, immunology, serology and NAT, vital signs measurements, and 12-lead ECG

results were also summarized descriptively.

Results:

Subject Disposition

Overall, in the safety lead-in and main study, 1267 subjects were enrolled and randomized (9 subjects and 1258 subjects, respectively).

Due to an error at the study site during the safety lead-in period, all 9 subjects received a single 2-g dose of CSL112 rather than the planned randomization schema of 3 active: 1 placebo. One subject died on Study Day 80 prior to completion of the final visit; the remaining 8 subjects completed the safety follow-up visit.

A total of 1258 subjects were enrolled and randomized in the main study, 419 subjects to the 2 g CSL112 treatment group, 421 subjects to the 6 g CSL112 treatment group, and 418 to the placebo treatment group. Within the Intent-to-Treat (ITT) population, 14 subjects (4 in the 2 g CSL112 group and 5 subjects each in the 6 g CSL112 and placebo groups) withdrew from the study before receiving IP and were therefore not included in the safety population. In the main study, only subjects who completed up to and including Visit 8 were considered to have completed the study irrespective of how many infusions of IP the subject received or which visit(s) was missed. Based on this definition, approximately 10% of subjects in each treatment group discontinued from the study; the primary reason was "other" in approximately (6%) of total subjects, with "subject decision" being the primary "other" reason. Approximately 91% of subjects overall completed all 4 infusions of IP.

Demographics

In the safety lead-in period, all subjects were white, and 7 of the 9 subjects (77.8%) were male; 77.8% were < 65 years of age (range: 52 - 71 years).

In the main study, all 3 treatment groups were generally well balanced in regards to demographic and other baseline characteristics. Approximately 97% of subjects were white, and approximately 80% were male. The mean age of subjects in this study was 58.3 years; the majority (approximately 72%) of subjects were less than 65 years of age, and few subjects (approximately 5%) were 75 years of age or older. Approximately half of the subjects in this study were from Eastern Europe.

Efficacy Results

This study was not powered for efficacy, and the efficacy endpoints for this study were either secondary or exploratory in nature.

- The number of MACE was low (n=74 [based on first events only and not including recurrent MACE]) overall, as was the number of subjects with complete follow-up through 1 year (n=89 [7.1%]), and time-to-first occurrence of MACE (from the date of randomization until the earliest date that any MACE endpoint was reached post randomization) showed no statistically significant difference in risk of the MACE secondary composite endpoint (CV death, nonfatal MI, ischemic stroke, and hospitalization for unstable angina) after administration of CSL112 as compared with placebo. However, the risk of experiencing the MACE composite secondary endpoint was numerically lower during the 3 to 4 months after administration of CSL112 6 g compared with CSL112 2 g or placebo.

- Although some favorable trends were observed for the CSL112 groups versus placebo for both the secondary and exploratory endpoints, the overall number of events was small, and the data did not allow for differentiation between treatment groups.

Pharmacokinetic Results

- After each IV infusion of CSL112 at doses of 2 g and 6 g, plasma concentrations of both apoA-I and PC rapidly increased, with dose-dependent, transient increases in systemic exposure.
- Within each CSL112 dose group, systemic exposure to apoA-I was greater after the fourth infusion relative to the first infusion, whereas systemic exposure to PC was similar after the fourth infusion relative to the first infusion.
- Plasma concentrations of apoA-I peaked at the end of each IV infusion of CSL112 (~2 hours), then declined in a biphasic manner to baseline in approximately 48 and 168 hours for the 2 g and 6 g dose groups, respectively.
- After the first and fourth infusion of a 6 g dose of CSL112, the terminal half-life ($t_{1/2}$) of apoA-I was approximately 54 and 104 hours, respectively.
- Plasma concentrations of PC peaked at the end of each IV infusion of CSL112 (~ 2 hours), then declined in a biphasic manner to baseline in approximately 24 hours for both doses of CSL112.
- Estimation of t½ for PC was variable.

Pharmacodynamic Results

- Following infusion of CSL112, total, ABCA1-independent, and ABCA1-dependent cholesterol efflux capacity of serum increased transiently in a dose-dependent manner.
- Following the first infusion of CSL112 (6 g), ABCA1-dependent cholesterol efflux capacity of serum increased 4-fold relative to baseline, whereas ABCA1-independent cholesterol efflux capacity of serum increased 2-fold relative to baseline.
- Cholesterol efflux capacity area under the effect time curve from time point zero (baseline) to the 24 hour time point ($AUEC_{0-24}$) was CSL112 dose- and apoA-I exposure (maximal response [R_{max}] and area under the effect time curve from baseline to the 24 hour time point [AUC_{0-24}])-linear.
- Dose-dependent elevations in HDL-cholesterol were maintained out to 48 hours and 96 hours for the CSL112 2 g and 6 g groups, respectively.
- No increases in atherogenic lipids / lipoproteins, including non-HDL-cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and triglyceride occurred after infusion of CSL112.
- CSL112 infusion had no effect on inflammatory (high sensitivity C-reactive protein, Interleukin 6, and fibrinogen), cardiovascular (troponin I, N-terminal pro b-type natriuretic peptide), or metabolic biomarkers (hemoglobin A1c).

Safety Results

Multiple (4, once-weekly) infusions of CSL112 at either 2-g or 6-g doses beginning within 7 days of an AMI and in close proximity to IV contrast agent administration (subjects who underwent angiography) were not associated with hepatic or renal safety concerns or any other significant safety concerns compared with placebo. No subjects fulfilled Hy's law criteria.

For the co-primary safety analysis of hepatic and renal endpoints:

- A total of 4 (1.0%), 2 (0.5%), and 0 subjects in the CSL112 2 g, CSL112 6 g, and placebo groups, respectively, had a laboratory value that met the hepatic co-primary endpoint
- A total of 0, 3 (0.7%), and 1 (0.2%) subjects in the CSL112 2 g, 6 g, and placebo groups, respectively, had a laboratory value that met the renal co-primary endpoint.
- For both the hepatic and renal co-primary endpoints, noninferiority to placebo was demonstrated, and neither of the dose comparisons were significantly different than placebo.

Other safety results were secondary and/or exploratory and included the following:

- Overall, the proportions of subjects who had at least 1 TEAE were comparable across the treatment groups, with approximately 50% of subjects in each treatment group reporting at least 1 TEAE during the main study. The majority of the TEAEs were CTCAE grade 1 or 2 in severity. Few Grade 4 or 5 TEAEs were reported (< 10 subjects in each treatment group).
- The most frequently reported TEAEs by SOC (≥10%) occurred in General Disorders and Administration Site Conditions (16.7%), Cardiac Disorders (11.2%), Gastrointestinal Disorders (10.5%), Respiratory, Thoracic and Mediastinal Disorders (10.2%) and Infections and Infestations (10%). The most frequently reported TEAEs (≥ 4% of subjects) in the combined CSL112 group included the following: chest pain (4.7%), angina pectoris (4.1%), dizziness (4.1%), dyspnea (4.0%), and diarrhea (4.0%). In the placebo group, diarrhea (4.1%) was the only TEAE reported in ≥ 4% of subjects.
- With the exception of General Disorders and Administration Site Conditions (2.1%), study drug-related TEAEs by SOC were all reported in < 2% of subjects overall. The only TEAEs related to IP that were reported in at least 1% of subjects in any treatment group (number [%] of subjects in the CSL112 2 g, CSL112 6 g, and placebo groups, respectively) were diarrhea (4 [1.0%], 3 [0.7%], 3 [0.7%] and headache (4 [1.0%,], 3 [0.7%], 0).
- The occurrence of suspected adverse drug reactions (as determined by FDA-specified criteria) was similar to that of most frequently reported TEAEs by SOC, with the most frequently reported (≥ 2%) as follows: General Disorders and Administration Site Conditions (8.8%), Nervous System Disorders (6.7%), Cardiac Disorders (5.5%), Infections and Infestations (4.0%), Respiratory, Thoracic and Mediastinal Disorders (4.0%), Vascular Disorders (2.8%), Musculoskeletal and Connective Tissue Disorders (2.6%) and Gastrointestinal Disorders (2.2%).

- Based on the FDA definition, suspected adverse drug reaction (ADR) preferred terms that were reported in approximately twice as many CSL112-treated subjects as in subjects who received placebo included the following (number [%] of subjects in the CSL112 2 g, CSL112 6 g, and placebo groups, respectively): cardiac failure (4 [1%], 6 [1.4%], 1 [0.2%]), myalgia (11 [2.7%], 9 [2.2%], 4 [1%]), headache (9 [2.2%], 16 [3.8], 5 [1.2]), dizziness (20 [4.8%], 14 [3.4%], and 9 [2.2%]), and urinary tract infection (7 [1.7%], 8 [1.9%], 1 [0.2%]).
- Of the 10 deaths that occurred during the main study (5 in the CSL112 2 g group, 4 in the CSL112 6 g group, and 1 in the placebo group), 6 were adjudicated as CV deaths by the CEC (2 cases of sudden death in the 2 g group; 2 cases of sudden death, 1 hemorrhagic stroke, and 1 undetermined cause of death in the 6 g group; and 0 CV deaths in placebo group). The 4 non-CV deaths included 3 in the 2 g group (hemorrhage, pulmonary and infection) and 1 in the placebo group (pulmonary). Despite the numeric imbalance between CSL112 and placebo groups, early clustering of the deaths or a pattern in regards to timing of the deaths was not observed.
- Serious adverse events reported in at least 1% of subjects in any treatment group included the following preferred terms (number [%] of subjects in the 2 g CSL112, 6 g CSL112, and placebo treatment groups): angina pectoris (5 [1.2%], 6 [1.4%], 5 [1.2%]); unstable angina (5 [1.2%], 3 [0.7%], 4 [1.0%]); chest pain (9 [2.2%], 4 [1.0%], 5 [1.2%]), and non-cardiac chest pain (2 [0.5%], 4 [1.0%], 4 [1.0%]). The proportion of subjects with at least 1 treatment-emergent serious adverse event (SAE) was highest in the CSL112 2 g group and comparable in the CSL112 6 g and placebo groups (15.9%, 12.7%, and 13.1%, respectively); however, the proportions of subjects who experienced individual SAEs were generally similar across treatment groups. Overall, SAEs were most commonly (≥ 5%) reported in the SOC of cardiac disorders (5.5%). The only other SOC having SAEs reported by ≥ 2% of subjects was general disorders and administrative site conditions (2.8% total).
- A numeric imbalance in the number of cases of heart failure as adjudicated by the CEC was also observed (5, 4 and 1 in the 2 g CSL112, 6 g CSL112 and placebo group, respectively). Overall, the etiology of the events was heterogeneous, and most events occurred early after the index MI, with a time course that is consistent with the pathophysiology of the underlying disease state. Two subjects, both in the CSL112 6 g group, were rechallenged with CSL112 without recurrence of heart failure. The small number of events precludes definitive determination of causality, and negative rechallenge in 2 subjects suggests that a causal relationship to CSL112 administration is not present.
- Headache, myalgia, urinary tract infection, injection/infusion site reactions, and venipuncture/catheter site reactions were determined to be ADRs for CSL112. Headache, injection and infusion site reactions, and venipuncture and catheter site reactions had already been identified as ADRs based on previously completed studies; myalgia (includes the PT myalgia) and urinary tract infection (includes the PTs urinary tract infection, cystitis and Escherichia urinary tract infection) were identified as new ADRs.

- The proportion of subjects who discontinued IP due to any TEAE was comparable in all 3 treatment groups. TEAEs of blood creatinine increased (0 subjects in the CSL112 2 g, 1 subject in the CSL112 6 g, and 2 subjects in the placebo groups), cardiac failure (2 subjects – CSL112 2 g group only), and hepatic function abnormal (1 subject each in the CSL112 2 g and placebo groups) were the only events that resulted in discontinuation of IP for more than 1 subject overall.
- Bleeding events were infrequent overall, with approximately 90% of subjects having experienced no bleeding events, and most bleeding events that did occur were not severe (ie, most were BARC Grade 1 or Grade 2).
- No subjects developed anti-CSL112 or anti-apoA-I antibodies.
- There was no definitive evidence of seroconversion by serology or NAT testing during the study.
- No patterns of changes in vital signs, ECGs, or other clinical laboratory tests were suggestive of an effect of CSL112 during the study.

Conclusions:

- CSL112 (apoA-I), at a dose of 2 g or 6 g, administered within 7 days of an acute MI as 4 single weekly infusions to subjects who were receiving standard of care therapy was well tolerated and not associated with significant alterations in liver or kidney function. The study co-primary safety endpoints were met.
- Overall, the rates of SAEs, AEs leading to discontinuation, and bleeding events of interest were low and comparable across all treatment groups.
- Infusion of CSL112 caused a dose-dependent elevation of both apoA-I and cholesterol efflux capacity; the cholesterol efflux response profile of subjects with AMI was consistent with previous studies of CSL112.
- The observed lipid and lipoprotein changes after CSL112 infusion demonstrated in this study are consistent with those previously observed in the CSL112 Phase 1 and Phase 2a studies.
- Based on these Phase 2b findings demonstrating the hepatic and renal safety of CSL112, further assessment of the clinical efficacy of CSL112 In an adequately powered Phase 3 study for the reduction of early recurrent CV events following acute MI is supported.

Date of Report: 24 January 2017