CLINICAL STUDY PROTOCOL

A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Investigate the Efficacy and Safety of CSL112 in Subjects with Acute Coronary Syndrome

Study Number:	CSL112_3001
Study Product:	CSL112 (apolipoprotein A-I [human])
Development Phase:	Phase 3
Sponsor:	CSL Behring LLC (CSLB) 1020 First Avenue King of Prussia PA 19406-0901
Protocol Version:	Amendment 1
EudraCT Number:	2017-000996-98
IND Number:	CCI
Protocol Date:	10 September 2019
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

List of Personnel and Organizations Responsible for Conduct of the Study

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the investigator's Study File. This list will be updated by CSLB (or delegate) and provided to the study sites as needed.

Revision History

Date	Version	Summary of Changes
23 January 2018	Original	Not applicable
10 September 2019	Amendment 1	• Modification of the primary endpoint to include all myocardial infarction (MI) events instead of only type 1 (spontaneous) MI events. • Modification of inclusion criterion 6 to limit to subjects that are at higher risk of an early recurrent cardiovascular event. • Inclusion of additional secondary and exploratory endpoints. • Specify that the 70% interim analysis will not be performed if the expected Independent Data Monitoring Committee (IDMC) review of the interim analysis is less than 2 months prior to the anticipated completion of enrollment. • Inclusion of the option to limit the number of subjects enrolled with a specific index MI type (ie, ST-segment elevation MI or non-ST-segment elevation MI). • Addition of recent nonclinical and clinical (ie, Study CSL112_1002) data. • Modification of wording associated with the following aspects of the study to provide clarification and improve protocol compliance: o Collection of concomitant medications related to acute coronary syndrome: timing during Follow-up Period. o Lipid panel tests: procedures to prevent unblinding. o Eligibility criteria: inclusion criteria 3, 5, and 7b and exclusion criteria 4 and 7c. o Angiography for treatment of the index MI: timing relative to randomization. o Stable renal function: inclusion of SI unit (µmol/L) values for serum creatinine. o Delayed infusions: study reference manual cited for additional guidance. o Measurement of creatinine: use of plasma or whole blood when serum creatinine testing is not available. o Suspected major adverse CV events reporting: events occurring before randomization not required to be reported for endpoint adjudication. o Potential hepatic injury: to be reported as an adverse event or serious adverse event as appropriate. o Acute kidney injury: laboratory abnormalities and associated conditions to be reported as an adverse event if deemed by the investigator as abnormal. • Minor corrections including changes for consistency, word modifications, and administrative changes.

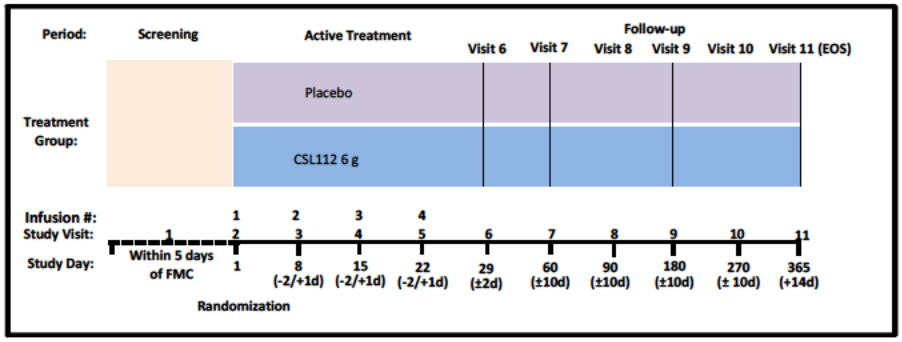
Protocol Synopsis

Title	A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Investigate the Efficacy and Safety of CSL112 in Subjects with Acute Coronary Syndrome
Study Number	CSL112_3001
Sponsor	CSL Behring LLC
Development Phase	Phase 3
Study Product	CSL112 (apolipoprotein A-I [apoA-I])
Indication	CSL112 is indicated to reduce the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in acute coronary syndrome (ACS) patients diagnosed with either ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI), and including those managed with percutaneous coronary intervention (PCI) or medically managed.
Study Summary and Overview	Acute coronary syndrome is a life-threatening condition, which most commonly occurs when an atherosclerotic plaque ruptures or erodes, leading to thrombus formation within a coronary artery. A thrombus within a coronary artery can result in unstable angina, MI, or sudden death. Even after recovery from an acute episode of ACS, patients continue to be at heightened risk. The risk of recurrent CV events is high despite advances in medical therapy and standard therapeutic regimens that have produced important improvements in the prognosis of patients with MI. CSL112 is a novel formulation of apoA-I, the major functional component of high-density lipoprotein. It is purified from human plasma, formulated to deliver exogenous apoA-I. Apolipoprotein A-I is formulated with phosphatidylcholine (PC) and stabilized with sucrose and cholate as excipients. CSL112 is being developed for use in patients with ACS (diagnosed with either STEMI or NSTEMI) to reduce the risk of CV death, MI, and stroke upon delivery of CSL112. Evidence from the Apo-I Event Reducing in Ischemic Syndromes-I (AEGIS-I) study has demonstrated that administration of apoA-I increases cholesterol efflux in MI patients. This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of CSL112 on reducing the risk of major adverse CV events

(MACE) in subjects with ACS (diagnosed with STEMI or NSTEMI), who are receiving evidence-based medical therapy.

Subjects will be randomized 1:1 to 1 of 2 treatment groups (CSL112 6 g or placebo). Randomization at baseline will be stratified by subjects' index MI type (STEMI vs NSTEMI), management of the index MI (PCI vs medically managed), and region (North America, Latin America, Western Europe, Central and Eastern Europe, or Asia Pacific). The study will consist of a Screening Period, an Active Treatment Period, and a Follow-up Period. Investigational product will be administered by intravenous (IV) infusion once weekly for 4 consecutive weeks. The primary efficacy outcome will be the composite of CV death, MI, or stroke from time of randomization through 90 days. Adverse event monitoring will continue through Visit 8 (Day 90), and all serious adverse events will be collected through the end of the study, regardless of relationship to investigational product. Subjects will be followed for occurrence of MACE for 365 days from randomization.

Synopsis Figure 1 Study Schema



EOS = End of Study; FMC = first medical contact.

Primary Objective(s)

The primary objective of this study is to evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) from the time of randomization through 90 days in subjects with ACS (diagnosed with STEMI or NSTEMI).

Primary Endpoint(s)

The primary endpoint is time to first occurrence of any component of the composite MACE, defined as CV death, MI, or stroke from the time of randomization through 90 days.

The primary endpoint will include all MIs.

Key Secondary Objective(s)	1. To evaluate the efficacy of CSL112 on reducing the total number of hospitalizations for coronary, cerebral, or peripheral ischemia. 2. To evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) through 180 and 365 days in subjects with ACS (diagnosed with STEMI or NSTEMI).
Key Secondary Endpoint(s)	1. Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days. 2. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 180 days. 3. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 365 days.
Other Secondary Objectives	1. To further evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) and all-cause death in subjects with ACS (diagnosed with STEMI or NSTEMI). 2. To evaluate the safety of CSL112 in subjects with ACS (diagnosed with STEMI or NSTEMI).
Other Secondary Endpoints	1. Time to first occurrence of each individual component of the composite primary efficacy endpoint from the time of randomization through 90 days: • CV death. • MI. • Stroke. 2. Time to first occurrence of CV death, type 1 MI, or stroke from the time of randomization through 90, 180, and 365 days. 3. Time to occurrence of all-cause death from the time of randomization through 365 days.
Exploratory Objective(s)	The exploratory objectives of this study are as follows: 1. To evaluate the efficacy of CSL112 on reducing the rate of hospitalization for coronary, cerebral, or peripheral ischemia. 2. To further explore the effect of CSL112 on the risk of MACE (CV death, MI, stroke), non-CV death, and severe coronary ischemia requiring urgent revascularization. 3. To assess the impact of CSL112 on medical resource utilization and quality of life. 4. To evaluate the pharmacokinetic / pharmacodynamic characteristics of CSL112.

Exploratory Endpoint(s)	The endpoints for evaluation of the exploratory objectives are: 1. Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 30 days. 2. Time to first occurrence of CV death, MI, stroke, or severe coronary ischemia requiring urgent revascularization from the time of randomization through 90 days. 3. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 30 and 60 days. 4. Time to first occurrence of MI by type, according to the universal definition, from the time of randomization through 90 days. 5. Time to occurrence of CV death from the time of randomization through 365 days. 6. Time to occurrence of non-CV death from the time of randomization through 365 days. 7. Total occurrence of re-hospitalization for CV events and all-cause death from the time of randomization through 90 days. 8. Total occurrence of CV death, MI, and stroke from the time of randomization through 90,180, and 365 days. 9. Total occurrence of all-cause death, MI, and stroke from the time of randomization through 90, 180, and 365 days. 10. Medical resource utilization from the time of randomization through 90 days: a. Number of total hospitalizations. b. Length of hospital stay. c. Number of critical care unit or intensive care unit days. d. Select procedures / surgeries related to hospitalization for coronary, cerebral, or peripheral ischemia. e. Discharge status to home with or without additional care, rehabilitation, and skilled nursing facilities following hospitalization for coronary, cerebral, or peripheral ischemia. 11. Change in EQ-5D-3L data from baseline to Day 90. 12. Pharmacokinetic endpoints will include the following: a. Baseline-corrected plasma apoA-I concentrations. b. Baseline-corrected plasma PC concentrations. c. Concentration in plasma at end of infusion for apoA-I and PC. d. Accumulation ratio for apoA-I and PC. 13. Pharmacodynamic endpoints include the following: a. Total cholesterol efflux.

	b. ABCA1-dependent efflux. c. ABCA1-independent efflux.
Number of Subjects	Approximately 17,400 subjects, with a maximum of 20,600 subjects, will be enrolled into this study.
Study Duration	The overall study duration (ie, first subject's Screening Visit to last subject's End of Study Visit) will be approximately 50 months.
Study Population and Main Criteria for Eligibility	1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements. 2. Male or female at least 18 years of age at the time of providing written informed consent. 3. Evidence of myocardial necrosis in a clinical setting consistent with type 1 (spontaneous) MI (STEMI or NSTEMI) caused by atherothrombotic coronary artery disease (4th Universal Definition of MI [Thygesen et al, 2019]) as defined by the following: a. Detection of a rise and / or fall in cardiac troponin I or T with at least 1 value above the 99th percentile upper reference limitAND b. Any 1 or more of the following: i. Symptoms of acute myocardial ischemia (ie, resulting from a primary coronary artery event). ii. New (or presumably new) significant ST/T wave changes or left bundle branch block. iii. Development of pathological Q waves on electrocardiogram. iv. Imaging evidence of new loss of viable myocardium or regional wall motion abnormality in a pattern consistent with an ischemic etiology. v. Identification of intracoronary thrombus by angiography. Note: Electrocardiograms obtained as part of standard of care can be used to support or confirm the index MI. 4. No suspicion of acute kidney injury at least 12 hours after IV contrast agent administration (subjects who have undergone angiography) or after first medical contact for the index MI (subjects who have not undergone angiography). There must be documented evidence of stable renal function defined as no more than an increase in serum creatinine < 0.3 mg/dL (27 μmol/L) from pre-contrast serum creatinine value. 5. Evidence of multivessel coronary artery disease defined as meeting 1 or more of the following criteria:

	a. At least 50% stenosis of the left main coronary artery or at least 2 epicardial coronary artery territories (left anterior descending, left circumflex, right coronary artery) on catheterization performed during the index hospitalization. b. Prior cardiac catheterization documenting at least 50% stenosis of the left main coronary artery or at least 2 epicardial coronary artery territories (left anterior descending, left circumflex, right coronary artery). c. Prior PCI and evidence of at least 50% stenosis of at least 1 epicardial coronary artery territory different from prior revascularized artery territory. d. Prior multivessel coronary artery bypass grafting. 6. Presence of established cardiovascular risk factor(s), defined as: a. Diabetes mellitus on pharmacotherapy. OR b. 2 or more of the following: i. Age ≥ 65 years. ii. Prior history of MI. iii. Peripheral arterial disease.
Study Product Dose, Dosing Regimen and Administration	The active component of CSL112 is apoA-I, which is purified from human plasma. Apolipoprotein A-I is formulated with PC and stabilized with sucrose and cholate as excipients. Reconstituted CSL112 (dose 6 g; approximately 170 mL) will be IV infused in a vein (peripheral or central) over 2 hours.
Comparator Product, Dose, Dosing Regimen and Administration	The placebo solution will comprise CCI [redacted] in water to yield a 4.4% albumin solution. An equivalent amount of placebo (approximately 170 mL) to CSL112 will be IV infused in a vein (peripheral or central) over 2 hours.
Efficacy Assessments	Efficacy assessments consist of any component of the primary, key secondary, other secondary, or exploratory composite MACE endpoints. All suspected efficacy endpoints / endpoint events or triggered requests for additional information will be reviewed and adjudicated by the Clinical Events Committee without unblinding treatment for confirming the occurrence of MACE.

Safety Assessments	Adverse event monitoring will be conducted from the time the subject gives informed consent through Visit 8 (Day 90). In addition, adverse events considered to be related to investigational product will be monitored through the End of Study Visit (Day 365). All serious adverse events will be collected through the end of the study, regardless of relationship to investigational product, and will be followed until the event resolves, stabilizes, or the subject is lost to follow-up. Blood for clinical laboratory testing (biochemistry panel and hematology) will be collected, and vital sign measurements will be conducted according to the Schedule of Assessments.
Pharmacokinetics	Plasma concentrations of apoA-I and PC will be assayed from the blood samples drawn in the planned pharmacokinetic substudy. Accordingly, blood samples will be drawn before infusion 1, end of infusion 1, and end of infusion 4.
Pharmacodynamics	Blood samples for pharmacodynamic assessments will be drawn at the same as time points as pharmacokinetic draws.
Other Assessments	Not applicable.
Statistical Analyses	The study is designed as a superiority study. The sample size calculation is based upon the hypothesis that compared with placebo, CSL112 will have a 20% relative risk reduction (hazard ratio = 0.80) in the primary endpoint over 90 days of follow-up after randomization (ie, all subjects will be followed for a fixed duration of 90 days after randomization). Assuming a 1-sided alpha of 0.025, not accounting for any dropouts from the study, and the specified interim analyses, 1004 confirmed MACE (CV death, MI, or stroke) will provide at least 90% power. A 1-sided hypothesis test is necessary to differentiate directionality for interim analyses of futility and efficacy. Based on an assumed 90-day placebo event rate of 6.4%, an estimated 17,400 subjects (8700 per group) will be required. The target number of events is also sufficient to achieve a 1-sided P value of 0.005 (approximate) with an observed hazard ratio of 0.85 in the primary endpoint and will afford at least 69% power to detect the minimally clinically relevant hazard ratio of 0.85. The primary endpoint is defined as time to first occurrence of the composite MACE (ie, CV death, MI, or stroke), from the time of randomization through 90 days. The primary endpoint will include all MIs. The primary analysis of time to the 3-component MACE (CV death, MI, or stroke) will be based on a covariate-adjusted Cox regression model including fixed effects for treatment, region, index MI type,

index MI management, age (as a continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and index MI management will be fitted using the PHREG procedure in SAS. The 1-sided Wald P value for hypothesis testing, the hazard ratio and its 2-sided 95% confidence interval, will be estimated from the model. The primary statistical analysis will utilize the Intent-to-treat (ITT) Analysis Set.

Additional sensitivity analyses of the primary endpoint will be performed to examine the robustness of the conclusion from the planned primary analysis to deviations from assumptions.

Statistical analysis of key secondary endpoints will be based on the ITT Analysis Set utilizing an overall, 1-sided 0.025 significance level. The hypotheses associated with the key secondary endpoints will be formally tested and therefore adjusted for multiplicity.

Interim Analyses

The sample size calculation given above for number of required events and number of estimated subjects includes 3 formal interim analyses. The first 2 interim analyses will be conducted for futility only after observation of approximately 301 confirmed MACE (30% of the total target number of events) and 502 confirmed MACE (50% of the total target number of events). The third interim analysis will be conducted for efficacy only after observation of approximately 703 confirmed MACE (70% of the total target number of events). Based on event accrual, if the expected timing of the Independent Data Monitoring Committee (IDMC) review of the 70% interim analysis is less than 2 months prior to the anticipated completion of study enrollment, the 70% interim analysis for efficacy will not be conducted.

Schedule of Assessments

Study Period	Ref. Section	Screening[A]	Active Treatment								Follow-up				
Infusion Number			1		2		3		4		NA	NA	NA	NA	NA	NA
Visit		1	2		3		4		5		6[B]	7[C]	8	9	10[C]	11 (EOS)
Day(s) (window)		-5 to -1	1 NA		8 (-2 / + 1)		15 (-2 / + 1)		22 (-2 / +1)		29 (± 2)	60 (± 10)	90 (± 10)	180 (± 10)	270 (± 10)	365 (+ 14)
Time relative to infusion		NA	SOI	EOI	SOI	EOI	SOI	EOI	SOI	EOI	NA	NA	NA	NA	NA	NA
ADMINISTRATIVE PROCEDURES																
Informed consent	4.1.1	X														
Informed consent for FBR (optional)[D]	8.3	X														
Medical and surgical history	8.1.1.1	X														
Prior / concomitant medication review	8.1.1.3	X	X		X		X		X		X	X	X	X[E]	X[E]	X[E]
Inclusion & exclusion criteria	4.1	X														
IRT subject registration, randomization, IP dispense[F]	6.1.2	X														
INVESTIGATIONAL PRODUCT INFUSION	6.2		X		X		X		X							
CLINICAL PROCEDURES																
Demography and height	8.1.1	X														
Vital signs	8.1.3.4	X	X		X		X		X		X					
Directed physical examination	8.1.1.2	X									X					
Body weight	8.1.1.2	X									X		X	X		X
Quality of life questionnaire: EQ-5D-3L	8.1.4.1	X											X			
Lifestyle adherence assessment	8.1.4.2												X	X		X
Adverse event monitoring	9	X	X	X	X	X	X	X	X	X	X	X	X	X[G]	X[G]	X[G]
Serious adverse event monitoring	9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endpoint (MACE) assessment[H]	8.1.2		X	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY PROCEDURES																
Pregnancy test (urine or serum; local)[I]	8.1.3.3	X									X					
ALT, total bilirubin (local; eligibility)[J]	8.1.3.2.1	X[J]														
Serum creatinine (local; eligibility)	8.1.3.2.1	X[K]			X[L,M]											
Biochemistry panel (central)	Table 3, 8.1.3.2.2		X[N]		X[M]		X[M]				X					
Hematology (central)	Table 3, 8.1.3.2.2		X[N]								X					
Immunogenicity (central)[O]	8.1.3.6		X[N]								X					
Parvovirus testing (central)[P]	8.1.3.5		X[N]								X					
FBR sample (central)[D,Q]	8.3		X[N]								X					
PK / PD sampling (at selected sites; central)	8.1.5		X	X						X						

ALT = alanine aminotransferase; central = central laboratory testing; EOI = end of infusion; EOS = End of Study; FBR = future biomedical research; HDL = High-density lipoprotein; IP = investigational product; IRT = interactive response technology; local = local laboratory testing; MACE = major adverse cardiovascular event; NA = not applicable; PD = pharmacodynamics; PK = pharmacokinetic; Ref. = reference; SOI = start of infusion.

Notes to the schedule of assessments:

A: A subject is considered eligible if they meet all inclusion criteria and none of the exclusion criteria. Screening and randomization may occur on the same day (Day 1) provided laboratory results are available for review by the investigator and eligibility criteria have been met for ALT, total bilirubin, and serum creatinine. Infusion 1 must be administered in the timeframe as detailed in Section 4.2.1.

B: Visit 6 should occur approximately 7 (± 2) days after infusion 4 (or last infusion). Subjects who prematurely discontinue infusion(s) of investigational product are to have Visit 6 / Early Termination Visit assessments as soon as possible after discontinuation of investigational product.

C: Visit 7 (Day 60) and Visit 10 (Day 270) assessments may be conducted either by telephone contact or face-to-face at the study site.

D: If a subject refuses consent for FBR sampling, or there is a documented law or regulation prohibiting sample collection, or if the Institutional Review Board / Independent Ethics Committee does not approve collection of the sample for these purposes, then the sample will not be collected at that site.

E: All concomitant treatments for ACS including the dose, route of administration, and frequency must be collected and monitored for change through to the EOS (Day 365).

F: At the Screening Visit, randomization in IRT will occur after eligibility criteria are met.

G: Only adverse events considered related to investigational product, leading to discontinuation of investigational product, and / or leading to withdrawal of consent during the study are to be collected at Visit 9 (Day 180), Visit 10 (Day 270), and EOS Visit (Day 365). Concomitant medications taken or administered for the treatment of such events are to be collected until resolution of the event.

H: If a subject has a suspected or confirmed stroke, the modified Rankin score should be obtained at the time of occurrence.

I: Only females of childbearing potential are to be tested; urine sample for local laboratory testing is the preferred method. If the urine test cannot be confirmed as negative, a serum pregnancy test will be required.

J: An elevation in ALT > 3 × upper limit of normal with a concomitant increase in total bilirubin that is > 2 × upper limit of normal should be reported as a serious adverse event within 24 hours.

K: Local laboratory values obtained as part of standard of care testing for the index acute myocardial infarction event and before obtaining written informed consent should be used to determine study entry and eligibility for infusion 1. However, if results (for ALT, total bilirubin and / or serum creatinine) are not available, then a blood sample must be obtained for the local laboratory testing.

L: **For subjects who received infusion 1 of investigational product > 12 hours and < 48 hours after IV contrast administration**: local laboratory serum creatinine value must be obtained before the infusion for comparison with the local laboratory baseline value and reviewed by the investigator. A blood sample for local laboratory testing to assess dosing eligibility for infusion 2 should not occur earlier than 72 hours following the infusion 1.

M: During study conduct, the Independent Data Monitoring Committee (IDMC) may make a recommendation to permit discontinuation of blood sampling at Visit 3 and Visit 4 for local laboratory and / or central laboratory biochemistry testing. If the IDMC so recommends, study investigators will be notified by the Executive Committee chairperson that these routine laboratory assessments are no longer required and eligibility for all subsequent infusions is to be based on clinical assessment (ie, starting with infusion 2 / Visit 3).

N: Blood sample is to be taken before the start of infusion. This blood sample must be sent to the central laboratory for study analysis purposes.

O: Blood samples are to be collected from all subjects at baseline and Visit 6 (Day 29). Immunogenicity testing will be performed using samples from approximately the first 600 subjects (approximately 300 CSL112 and 300 placebo) and oversight will be provided by the IDMC (Section 8.1.3.6).

P: Blood samples are to be collected from all subjects at baseline and Visit 6 (Day 29). Nucleic acid testing and serology (parvovirus B19) will be performed using samples from approximately 300 randomly selected subjects (approximately 150 CSL112 and150 placebo).

Q: Future biomedical research testing includes samples collected at baseline that are intended for storage and / or future analyses (eg, pharmacogenomics).

Note: Assessments are to be conducted at all times and days that are marked with an X. **The investigator and other blinded study staff must not review the results of a lipid panel test (specifically the HDL cholesterol level) during the Active Treatment Period as the results may unblind treatment assignment.**

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List of Abbreviations

Abbreviation	Term
ACC / AHA / ESC	American College of Cardiology / American Heart Association / European Society of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
AE	Adverse event
AESI	Adverse event of special interest
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
apoA-I	Apolipoprotein A-I
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
CCU	Critical care unit
CEC	Clinical Events Committee
CSLB	CSL Behring
CV	Cardiovascular
CCI	Dextrose 5% in water
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
FBR	Future biomedical research
FDA	US Food and Drug Administration
FMC	First medical contact
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDL	High-density lipoprotein
HF	Heart failure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A

Abbreviation	Term
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
MACE	Major adverse cardiovascular event(s)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified Intent-to-treat
NA	Not applicable
NOAEL	No observed adverse effect level
NSTEMI	Non-ST-segment elevation myocardial infarction
PC	Phosphatidylcholine
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Queries
STEMI	ST-segment elevation myocardial infarction
ULN	Upper limit of normal
VAS	Visual analog scale

1 Introduction

1.1 Background

Cardiovascular (CV) disease is the leading global cause of death, accounting for 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. There are more deaths annually from CV disease causes than all forms of cancer combined [Mozaffarian et al, 2016]. The disease process responsible for the majority of CV disease-related deaths is atherosclerosis, which can lead to a variety of acute presentations depending on the arterial bed affected and severity; the 2 most common are acute coronary syndrome (ACS) and ischemic stroke [Mahoney et al, 2008].

Acute coronary syndrome is a life-threatening condition, which most commonly occurs when an atherosclerotic plaque ruptures or erodes, leading to thrombus formation within a coronary artery. A thrombus within a coronary artery can result in unstable angina, a myocardial infarction (MI) (heart attack), or sudden death. Even after recovery from an acute episode of ACS, patients continue to be at heightened risk. The short-term morbidity and mortality associated with both the index coronary event and recurrent CV events can be as high as 20% per year [Morrow, 2010]. In the PLATO Study, which was conducted in ACS patients, approximately 50% of recurrent CV events (CV death, MI, or stroke) occurred within the first 30 days of a 1-year follow-up period in all ACS subgroups [NDA 22-433/S015 Brilinta®, 2015].

Despite advances in therapeutic strategies for ACS, patients remain at heightened risk for recurrent ischemic events, particularly in the immediate weeks to months following the event. Consequently, effective and safe therapies that provide clinically relevant reductions in recurrent CV events beyond current secondary prophylaxis are needed for patients with ACS.

High-density lipoprotein (HDL) exerts a protective effect in experimental models of atherosclerotic CV disease. While the proposed atheroprotective properties of HDL are multifaceted [Remaley et al, 2008; Tardif et al, 2009], HDL is believed to bring about beneficial effects mainly by reverse cholesterol transport, whereby excess cholesterol is removed from arteries containing atherosclerotic plaques and transported back to the liver for excretion. This removal of cholesterol is mediated by the dominant protein of HDL, apolipoprotein A-I (apoA-I) [Tall, 1998], and removal of cholesterol from the artery wall reduces the size of the plaque. Cholesterol efflux capacity, an ex vivo measure of HDL function, evaluates the ability of HDL to remove excess cholesterol from atherosclerotic plaque for transport to the liver. The measure is a correlate of major adverse CV events

(MACE) endpoints that is independent of HDL cholesterol [Khera et al, 2011; Rohatgi et al, 2014; Saleheen et al, 2015; Liu et al, 2016; Zhang et al, 2016]. It has been suggested that pharmacotherapies that elevate cholesterol efflux capacity may be more likely to yield benefit to patients than those which raise HDL cholesterol [Siddiqi et al, 2015]. The central hypothesis of the program is that elevation of cholesterol efflux by infusion of CSL112 will reduce recurrent events in the period of high risk following an MI.

1.2 Background Information on CSL112

1.2.1 Overview

CSL112 is a novel intravenous (IV) formulation of apoA-I purified from human plasma, formulated to deliver exogenous apoA-I. It is being developed for use in patients with ACS (diagnosed with either ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) to reduce the risk of CV death, MI, and stroke upon delivery of exogenous apoA-I. The formulation of CSL112 includes apoA-I (active), phosphatidylcholine (PC), sodium cholate, and sucrose.

A detailed description of the chemistry, pharmacology, efficacy, and safety of CSL112 is provided in the Investigator Brochure.

1.2.2 Nonclinical Evaluation

CSL112 single and repeat dose nonclinical safety studies have been conducted. In single-dose studies (CSL112 administered as an IV infusion of 1-hour duration), a no observed adverse effect level (NOAEL) of 300 mg/kg was established in both rats and cynomolgus monkeys. In repeat-dose studies (CSL112 administered once every 3 days for 4 weeks by IV infusion), a NOAEL of 80 mg/kg was established in rats; however, a NOAEL was not established in the cynomolgus monkey because some adverse effects were observed at the lowest dose tested (80 mg/kg). In a 13-week repeat-dose toxicity study in rats (CSL112 administered by IV infusion over 2 hours, once every 3 days for 13 weeks), a NOAEL of 320 mg/kg was established. The higher NOAEL established in this longer term study, which indicates improved tolerability, reflects the transient nature of the effects observed with 4-week repeat dosing in rats. No treatment-related deaths occurred in any of the toxicity studies.

After IV infusion of CSL112 to both rats and monkeys, the primary toxicological effects were hepatic and hematologic in nature. The effects were generally reversible, asymptomatic, and exhibited a moderate dose-response relationship. Some minor effects on renal parameters

were also observed; however, as there were no correlative histopathology findings in the kidney, the toxicological significance is unclear.

The reproductive toxicity of CSL112 has been evaluated in embryo-fetal development studies in rats and rabbits; results from the embryo-fetal development study in rabbits indicate that CSL112 potentially represents a significant risk to the human fetus. Therefore, additional screening for pregnancy and highly effective contraception methods are necessary in clinical studies. No fertility studies have been conducted for CSL112; however, after repeat dosing, no treatment-related macroscopic or microscopic effects have been observed in reproductive organs of rats or cynomolgus monkeys.

Further details on the hepatic and hematologic effects in the nonclinical studies, as well as other observations with CSL112, can be found in the Investigator Brochure for CSL112.

1.2.3 Clinical Experience

In total, 1060 subjects have received at least 1 infusion of CSL112 in 7 completed clinical studies. Two phase 1 studies (Study CSLCT-HDL-09-63 and Study CSLCT-HDL-10-68), which were conducted in healthy adults, evaluated the safety, tolerability, and pharmacokinetics (PK) of escalating single or multiple doses of CSL112 [Gille et al, 2014]. A third phase 1 study (Study CSL112_1001) evaluated CSL112 in healthy adult subjects with normal renal function and adult subjects with moderate renal impairment. A fourth phase 1 study (CSL112_1002) evaluated a single dose of CSL112 in healthy Japanese adults and weight-matched Caucasian adults. A phase 2a clinical study (Study CSLCT-HDL-10-70a) was conducted in subjects diagnosed with stable atherothrombotic disease, ie, the target population after initial acute presentation. A phase 2b study (Study CSLCT-HDL-12-77; AEGIS-I) [Gibson et al, 2016] evaluated CSL112 in MI subjects who were at high risk of subsequent CV events and had either normal renal function or mild renal impairment. The subjects enrolled in AEGIS-I were representative of the target phase 3 population in age, sex, concurrent medical conditions (eg, diabetes, hypertension), and chronic concomitant medications (eg, dual anti-platelet therapy, statins). A phase 2 study (Study CSL112_2001) was conducted in subjects with acute myocardial infarction (AMI) and moderate renal impairment. The safety profile, PK, and cholesterol efflux response were comparable to results demonstrated in the CSLCT-HDL-12-77 (AEGIS-I) clinical trial.

1.3 Study Overview

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of CSL112 on reducing the risk of MACE in

subjects with ACS, who are receiving evidence-based medical therapy. Subjects who present with STEMI or NSTEMI (managed with percutaneous coronary intervention [PCI] or medically managed), with documented evidence of multivessel coronary artery disease and other established risk factor(s) for recurrent CV events [Amsterdam et al, 2014; O'Gara et al, 2013], were selected as the study population because they are all at high risk for recurrent MACE after experiencing an index event. The study will enroll approximately 17,400 subjects with recent MI, up to approximately a maximum of 20,600 subjects, who will be randomized with equal allocation (1:1 ratio) to 1 of 2 treatment groups (CSL112 6 g or placebo). Randomization at baseline will be stratified by subject's index MI type (STEMI vs NSTEMI), management of the index MI (PCI vs medically managed), and region (North America, Latin America, Western Europe, Central and Eastern Europe, or Asia Pacific). Investigational product will be administered by IV infusion once weekly for 4 consecutive weeks. The primary efficacy outcome will be the composite of CV death, MI, or stroke from the time of randomization through 90 days. Subjects will be followed for occurrence of MACE for 365 days from randomization.

1.4 Potential Risks and Benefits

After an ACS event, patients are at risk of important additional clinical events such as death, MI, and stroke that could potentially be improved by treatment with CSL112. Six months after patients present with an index event of STEMI, approximately 15% will either have died or had another episode of myocardial ischemia, and a similar situation exists for NSTEMI / unstable angina patients [Yusuf et al, 2006]. Approximately half of these events will occur within the first 30 days after randomization [Wallentin et al, 2009]. It is hypothesized that infusion of CSL112 will provide therapeutic benefit to patients with recent MI who are at particularly high risk for early recurrent CV events.

CSL112 contains sucrose as a stabilizer. Administration of sucrose by IV infusion has been associated with reports of acute kidney injury (AKI) attributed to osmotic nephrosis when immune globulin IV products formulated with sucrose were administered at high doses or at high rates of administration [Epstein and Zoon, 2000]. The dose of sucrose in a 6 g dose of CSL112 is approximately 2.5-fold less than the lowest single dose of sucrose that was associated with histopathologic changes in the kidney but without clinical evidence of nephrotoxicity. In addition, the maximum infusion rate for CSL112 of 6 g/2 hours (50 mg/min) ensures a sucrose infusion rate of < 1.7 mg sucrose/kg/min for an adult weighing 50 kg, which is well within the published guideline for safe administration of sucrose-containing immune globulin IV products [Epstein and Zoon, 2000]. In AEGIS-I, the co-primary endpoint of renal safety was demonstrated in subjects with an estimated

glomerular filtration rate (eGFR) ≥ 60 mL/min/m^2 who received the first dose of CSL112 at least 12 hours but no later than 7 days after the index MI. Renal safety was demonstrated in subjects with moderate renal impairment eGFR < 60 and ≥ 30 mL/min/m^2 in the CSL112_2001 study.

CSL112 was formulated to contain lower PC and cholate levels than its predecessor formulation, CSL111. The intent of the reformulation was to mitigate the treatment-emergent, reversible, asymptomatic elevations in aminotransferases and unconjugated bilirubin that were noted with CSL111 in a phase 2a study conducted in MI subjects [Tardif et al, 2007]. In addition, the sucrose content was reduced in CSL112 to mitigate any potential renal safety issues. No renal or hepatic safety signals were identified with administration of CSL112 (2 g or 6 g) in the AEGIS-I study or in the phase 2 safety study in AMI with moderate renal impairment (6 g dose of CSL112).

There is a potential for allergic reactions or hypersensitivity to CSL112 in certain individuals, given the constituents of the product. CSL112 consists of apoA-I purified from human plasma. To date, CSL112 has been evaluated in 1060 subjects who have been exposed to at least 1 dose of CSL112 without the occurrence of product-specific antibodies. CSL112 may contain immunoglobulin A (IgA) and also contains PC derived from soy beans. Therefore, subjects with a positive history of IgA deficiency, antibodies to IgA, or allergy to either soy bean or peanuts will be excluded from the study. In AEGIS-I, drug hypersensitivity reactions primarily consisting of rash were reported with similar frequency amongst treatment groups (all CSL112: 3.0%; placebo: 2.7%), and no anaphylaxis / anaphylactoid reactions were reported.

The risk of viral and prion contamination is a feature common to all biologic agents in which the manufacture involves the use of materials of animal or human origin and CSL112, therefore, may carry a risk of transmitting infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease agent). However, the risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including steps for virus inactivation, and sterility in the manufacturing process. In the development program, there was no evidence of exposure to viral contamination in subjects exposed to CSL112.

Overall, the safety and tolerability profiles of CSL112 have been acceptable.

A low dose of albumin will be used as the matching placebo. Albumin in therapeutic doses can be used as a volume expander in states of low intravascular volume and is

contraindicated in patients with cardiac failure. The use of 170 mL of a 4.4% albumin solution infused over 2 hours in hemodynamically stable, compensated ACS subjects is anticipated to have a negligible impact on plasma osmolality. The risk of anaphylaxis or other severe hypersensitivity reactions is anticipated to be very low based on post-marketing data and medical literature. All subjects will be monitored for the potential risk of hypersensitivity. Albumin in varying doses has been used as placebo in various non-CV disease states and was well tolerated [Chenevard et al, 2012; Relkin et al, 2017, Gelmont et al, 2016; Finfer, 2014]. Based on internal assessment and validation from external advisors such as the AEGIS-II Executive Committee and the Independent Data Monitoring Committee (IDMC), the use of albumin as placebo in a low concentration infused over a 2-hour period is anticipated to be well tolerated in compensated ACS subjects.

Subjects in clinical studies generally cannot expect to receive direct benefit from treatments during participation as clinical studies are designed to provide information about safety and efficacy of a new investigational product. Additional details about CSL112 can be found in the current version of the Investigator Brochure for CSL112 which outlines the potential risks to subjects administered CSL112 and precautions for its use.

Thus, given the potential benefit of CSL112 and the acceptable safety profile of CSL112 and low dose albumin (as placebo), justification is provided for the clinical trial, which will evaluate the use of CSL112 in the reduction of early MACE in a high-risk ACS population.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoint

The primary objective of this study is to evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) from the time of randomization through 90 days in subjects with ACS (diagnosed with STEMI or NSTEMI).

Primary Efficacy Endpoint	**Summary Measures**
Time to first occurrence of any component of composite MACE, defined as CV death, MI, or stroke from the time of randomization through 90 days. The primary endpoint will include all MIs.	Event rate (%) at 90 days by treatment arm. Point estimate and 95% CI for hazard ratio (CSL112:Placebo).

CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction.

2.2 Secondary Objectives and Endpoints

2.2.1 Key Secondary Objectives

The secondary objectives of this study are as follows:

1. To evaluate the efficacy of CSL112 on reducing the total number of hospitalizations for coronary, cerebral, or peripheral ischemia.
2. To evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) through 180 and 365 days in subjects with ACS (diagnosed with STEMI or NSTEMI).

2.2.2 Key Secondary Endpoints

Key secondary efficacy endpoints are those for which the associated hypotheses will be formally tested and are therefore adjusted for multiplicity.

Key Secondary Objective	Key Secondary Endpoints	Summary Measure(s)
1	Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days.	• Mean hospitalization rate per 90 days by treatment arm. • Point estimate and 95% CI for Rate ratio (CSL112:Placebo).
2	Time to first occurrence of CV death, MI, or stroke from the time of randomization through 180 days.	• Event rate (%) at 180 days by treatment arm. • Point estimate and 95% CI for hazard ratio (CSL112:Placebo).
	Time to first occurrence of CV death, MI, or stroke from the time of randomization through 365 days.	Event rate (%) at 365 days by treatment arm • Point estimate and 95% CI for hazard ratio (CSL112:Placebo)

CV = cardiovascular; MI = myocardial infarction.

2.2.3 Other Secondary Objectives

Other secondary objectives of the study are as follows:

1. To further evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) and all-cause death in subjects with ACS (diagnosed with STEMI or NSTEMI).
2. To evaluate the safety of CSL112 in subjects with ACS (diagnosed with STEMI or NSTEMI).

2.2.4 Other Secondary Endpoints

2.2.4.1 Other Secondary Efficacy Endpoints

Other Secondary Efficacy Endpoints	Summary Measure(s)
Time to first occurrence of each individual component of the composite primary efficacy endpoint from the time of randomization to 90 days: • CV death. • MI. • Stroke.	For each component: • Event rate (%) at 90 days by treatment arm. • Point estimate and 95% CI for hazard ratio (CSL112:Placebo).
Time to first occurrence of CV death, type 1 MI, or stroke from the time of randomization through 90, 180, and 365 days.	• Event rate (%) at 90, 180, and 365 days by treatment arm. • Point estimate and 95% CI for hazard ratio (CSL112:Placebo).
Time to occurrence of all-cause death from the time of randomization through 365 days.	• Event rate (%) at 365 days by treatment arm. • Point estimate and 95% CI for hazard ratio (CSL112:Placebo).

CV = cardiovascular; MI = myocardial infarction.

2.2.4.2 Other Secondary Safety Endpoints

Other Secondary Safety Endpoints	Summary Measure(s)
Adverse Events.	• Overall n (%) of subjects with adverse events through 90 days. • Overall n (%) of subjects with treatment-related adverse events through End of Study (EOS). • Overall n (%) of subjects with SAEs through EOS.
Changes in clinical laboratory assessments.	• Descriptive statistics for actual value and change from baseline. • n (%) of subjects with a shift from baseline to worst post-treatment value according to normal range criteria (normal, high, or low).

EOS = End of Study; SAE = serious adverse event.

2.3 Exploratory Objectives and Endpoints

2.3.1 Exploratory Objectives

The exploratory objectives of this study are as follows:

1. To evaluate the efficacy of CSL112 on reducing the rate of hospitalization for coronary, cerebral or peripheral ischemia.

2. To further explore the effect of CSL112 on the risk of MACE (CV death, MI, stroke), non-CV death, and severe coronary ischemia requiring urgent revascularization.
3. To assess the impact of CSL112 on medical resource utilization and quality of life.
4. To evaluate the PK / pharmacodynamic (PD) characteristics of CSL112.

2.3.2 Exploratory Endpoints

The endpoints for evaluation of the exploratory objectives are:

1. Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 30 days.
2. Time to first occurrence of CV death, MI, stroke, or severe coronary ischemia requiring urgent revascularization from the time of randomization through 90 days.
3. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 30 and 60 days.
4. Time to first occurrence of MI by type, according to the universal definition, from the time of randomization through 90 days.
5. Time to occurrence of CV death from the time of randomization through 365 days.
6. Time to occurrence of non-CV death from the time of randomization through 365 days.
7. Total occurrence of re-hospitalization for CV events and all-cause death from the time of randomization through 90 days.
8. Total occurrence of CV death, MI, and stroke from the time of randomization through 90, 180, and 365 days.
9. Total occurrence of all-cause death, MI, and stroke from the time of randomization through 90, 180, and 365 days.
10. Medical resource utilization from the time of randomization through 90 days:
    a. Number of total hospitalizations.
    b. Length of hospital stay.
    c. Number of critical care unit (CCU) or intensive care unit (ICU) days.
    d. Select procedures / surgeries related to hospitalization for coronary, cerebral, or peripheral ischemia.

e. Discharge status to home with or without additional care, rehabilitation, and skilled nursing facilities following hospitalization for coronary, cerebral, or peripheral ischemia.

11. Change in EQ-5D-3L data from baseline to Day 90.
12. Pharmacokinetic endpoints will include the following:
    a. Baseline-corrected plasma apoA-I concentrations.
    b. Baseline-corrected plasma PC concentrations.
    c. Concentration in plasma at end-of infusion for apoA-I and PC.
    d. Accumulation ratio for apoA-I and PC.
13. Pharmacodynamic endpoints include the following:
    a. Total cholesterol efflux.
    b. ABCA1-dependent efflux.
    c. ABCA1-independent efflux.

3 Study Overview

3.1 Study Design

This is a phase 3 multicenter, double-blind, randomized, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of CSL112 on reducing the risk of MACE in subjects with ACS (diagnosed with STEMI or NSTEMI) who are receiving evidence-based medical therapy.

Subjects will be screened and, if eligible, stratified at baseline by index MI type (STEMI vs NSTEMI), management of the index MI (PCI vs medically managed), and region (North America, Latin America, Western Europe, Central and Eastern Europe, or Asia Pacific). A balanced distribution of STEMI and NSTEMI is desired, and may require implementation of a limit on an index MI type during the conduct of the study. The study will enroll approximately 17,400 subjects with recent MI, up to a maximum of approximately 20,600 subjects, who will be randomized with equal allocation (1:1 ratio) to 1 of 2 treatment groups (CSL112 6 g or placebo).

The study is planned to be conducted at approximately 1000 sites. The estimated study duration is approximately 50 months.

The study will consist of a Screening Period, an Active Treatment Period, and a Follow-up Period (Figure 1).

First medical contact (FMC) is defined as the documented time point (ie, clock start) when the subject arrives at the 1st treating hospital emergency department (ie, door time) or cardiac catheterization laboratory for evaluation and treatment of the index MI event. Eligible subjects meeting all inclusion criteria and none of the exclusion criteria (Section 4.1), and who meet dosing eligibility criteria (Section 4.2) will receive once weekly IV infusions of investigational product (CSL112 or placebo) for 4 consecutive weeks, with each infusion approximately 7 days apart (- 2 / + 1; ie, dosing between 5 to 8 days window) during the 4-week Active Treatment Period. Each infusion of investigational product should be completed as close to the visit windows outlined in the Schedule of Assessments as possible. An infusion may be skipped (ie, 'missed') or delayed at the discretion of the investigator to evaluate and treat an adverse event (AE) before the next infusion. Therefore, the time window between each infusion may be extended as long as the last infusion of investigational product is given within 30 days of infusion 1, and the minimum window between infusions is at least 5 days.

For all randomized subjects, before administration of infusion 1 of investigational product, each subject must be deemed clinically stable, must meet the renal and hepatic eligibility criteria, and be dosed within 5 days of FMC. In addition:

- For subjects treated medically with or without thrombolytic agents, infusion 1 of investigational product must occur no earlier than 12 hours after FMC.
- For subjects undergoing angiography or PCI, with or without stent placement, infusion 1 of investigational product must occur no earlier than 12 hours after IV contrast administration.

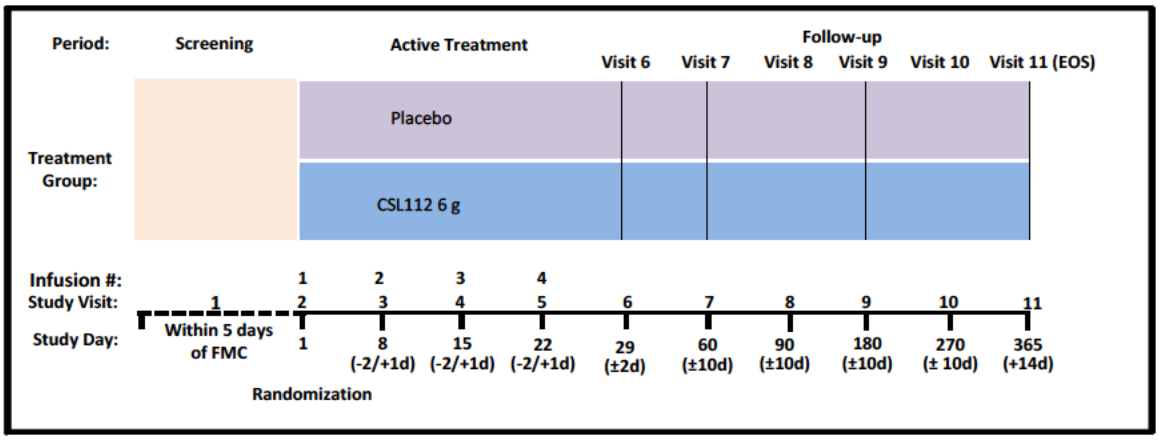
Infusion 1 should occur before hospital discharge or on the day of discharge. If discharge occurs on a weekend, infusion 1 of investigational product can be administered on the next business day as long as timing is still within 5 days of FMC. All tests and procedures that are required to be performed to determine subject eligibility (ie, screening and randomization) must be performed with enough time to administer the investigational product within this timeframe. Screening and randomization may occur on the same day (Day 1) provided laboratory results are available for review by the investigator and all eligibility criteria have been met, including the requirements for alanine aminotransferase (ALT), total bilirubin, and serum creatinine.

Study assessments will be conducted at screening (Visit 1), before and after infusions (Days 1, 8, 15, and 22 [Visits 2, 3, 4, and 5, respectively]), at Day 29 / Visit 6 (end of Active Treatment Period), Day 60 / Visit 7, Day 90 / Visit 8, and every 90 days thereafter up to Day 365 (Figure 1). During the Follow-up Period, the Day 60 / Visit 7 and Day 270 / Visit 10 assessments may be conducted by telephone. All other visits during the Follow-up Period will be conducted as in-person visits at the clinical site. The study will conclude at least 365 days after the last subject is randomized. Study assessments will be conducted as shown in the Schedule of Assessments.

Interim analyses for futility and efficacy will be conducted at scheduled intervals, and safety reviews will be performed periodically by the IDMC. These formal interim analyses will be performed at times based on accrual of the adjudicated primary 90-day MACE. Three planned interim analyses will be performed after observation of approximately 30%, 50%, and 70% of the event target for the primary MACE endpoint; the first and second interim analyses will be for futility only while the third interim analysis will be for efficacy only (Section 10.3.6). As part of the IDMC charter, criteria will be specified for early termination of the study for futility and efficacy. Based on event accrual, if the expected timing of the IDMC review of the 70% interim analysis is less than 2 months prior to the anticipated completion of study enrollment, the 70% interim analysis for efficacy will not be conducted.

During the course of study conduct, the IDMC will assess safety with respect to hepatic and renal function when the first 20% of enrolled subjects have completed Visit 6 (Day 29). In addition, the IDMC will review renal function for those subjects dosed within 12 to < 48 hours after contrast administration (see Section 10.3.6.2 for further details).

Figure 1 Study Schema



EOS = End of Study; FMC = first medical contact.

3.2 Dose and Dosing Regimen

CSL112 (6 g) or a matched volume of placebo will be administered as an IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (4 infusions total) (Section 6.2). The placebo used in this study is a physical match to the investigational product, CSL112, (Section 5.1.2) after proper preparation. A 6 g dose of CSL112 was selected for this study based upon the safety and PK / PD data obtained in the AEGIS-I study in subjects with MI (Study CSLCT-HDL-12-77).

Dosing eligibility criteria are presented in Section 4.2.

3.3 Scientific Rationale

3.3.1 Study Design Rationale

Despite advances in therapeutic strategies for ACS, patients are at high risk for early recurrent events, particularly in the immediate weeks to months following the event. Consequently, effective and safe therapies that provide clinically relevant reductions in recurrent CV events beyond current secondary prevention are needed for patients with ACS. Subjects with a recent MI have been chosen as the study population to best study this unmet need in the immediate weeks to months following the event. In addition to the key inclusion criterion of evidence of multivessel coronary artery disease (see Section 4.1.1, Inclusion Criterion 5), subjects are required to have the presence of high cardiovascular risk, either the presence of diabetes mellitus requiring pharmacotherapy or at least 2 of the following risk factors: age of 65 years or older, prior history of MI, or peripheral arterial disease. This enrichment strategy selects subjects at highest risk for subsequent CV events after an MI and provides adequate representation of subgroups of interest.

A double-blind design is being used to avoid potential bias during data collection and evaluation of clinical endpoints. A placebo-controlled design is being used because there is no approved active comparator for CSL112; therefore, CSL112 will be evaluated compared with placebo. All subjects randomized to treatment (CSL112 or placebo) in the study will receive background evidence-based medical therapy according to local standards of care and national practice guidelines (without a local standard, the current guideline from the American College of Cardiology / American Heart Association, European Society of Cardiology, etc. should be utilized), which will allow assessment of the incremental impact of CSL112 over currently approved treatments.

The definition of FMC has been selected to best represent the time the subject first presents for treatment for an acute ACS event and allows for targeted treatments to be provided. The goals of early treatment are immediate relief of ischemia, and prevention of complications arising from the MI and death. Thus, the time period of FMC is the start of the observation when acutely targeted therapies can be administered. This time period best allows for the identification of patients who have clinical instability and do not meet eligibility criteria. All patients who are deemed clinically stable during this period, have no suspicion of AKI after IV contrast agent administration (subjects who have undergone angiography) or after FMC for the index MI (subjects who have not undergone angiography), and meet all eligibility criteria should be considered for participation in the clinical trial. In contrast to acute ACS therapies, CSL112 is being developed for use in high-risk ACS patients to reduce the risk of CV death, MI, and stroke during the sub-acute period post MI when patients continue to be at increased risk for recurrent events.

Because of the related pathophysiology of individual CV events such as death, MI, and stroke after the acute phase of ACS, composite MACE endpoints consisting of relevant and related components have become accepted as primary endpoints in the study of new agents in ACS studies [CPMP/EWP/570/98, 2016]. Cardiovascular death, MI, and stroke are the most clinically meaningful efficacy endpoints for CV clinical studies as they are distinct irreversible events. The treatment focus for CSL112 is the subacute (ie, short term) period when patients recovering from ACS are most vulnerable for recurrent events. Therefore, to assess clinical benefit of CSL112, the primary endpoint of MACE at Day 90 is an appropriate timepoint. The durability of CSL112 will be assessed using the key secondary endpoints of MACE at Day 180 and extended follow-up at Day 365.

3.3.2 Dose Rationale

A 6 g dose of CSL112 was selected for this study based upon results from a PK-PD model that was developed to assess the relationship between apoA-I exposure and cholesterol efflux capacity using data from the AEGIS-I study in subjects with MI:

- The 6-g dose demonstrated an immediate 4-fold increase in cholesterol efflux capacity and 2-fold elevation in apoA-I compared with baseline. The 6-g dose can achieve the highest and most immediate elevation of cholesterol efflux capacity that can be practically obtained in MI subjects without compromising subject safety.
- The interval between infusions was chosen to maximize continuous exposure to the drug substance, apoA-I, above baseline levels and to minimize net accumulation of either apoA-I or its phospholipid excipient.

- The choice of 4 infusions is based on the rapid decline in risk in the month after an MI, such that the potential value to the subject for subsequent infusions diminishes each week after MI as the potential risk also decreases.

In AEGIS-I and CSL112_2001 studies, hepatic and renal safety were demonstrated in subjects with an eGFR ≥ 30 mL/min/m^2 who received the first 6 g dose of CSL112 at least 12 hours but no later than 7 days after an MI and 3 subsequent infusions at least 5 days apart. The type and frequency of AEs reported in AEGIS-I and CSL112_2001 are consistent with that reported in the early phase studies conducted in healthy adults, stable patients with atherothrombotic disease and stable patients with mild renal impairment.

3.4 Planned Study Duration

The duration of the study for an individual subject is expected to be approximately 365 days (+ 14 days). This estimation is based on:

- A Screening Period of up to 5 days from FMC.
- An Active Treatment Period of 5 weeks (includes maximum window at each visit): 4 infusions of investigational product administered approximately 7 days apart.
- A Follow-up Period of approximately 11 months (ie, to Day 365).

The overall study duration (ie, first subject's Screening Visit to last subject's EOS Visit) will be approximately 50 months.

3.5 Planned Number of Subjects

An estimated 17,400 subjects will be enrolled. MACE rates will be monitored using blinded data on an ongoing basis during the enrollment phase of the study to determine the actual number of subjects to be enrolled. A sample size of up to approximately 20,600 subjects will be permitted without a protocol amendment (Section 10.1).

3.6 Definition of End of the Clinical Study

The end of the clinical study (ie, completion of the study at all participating study sites) will be at least 365 days after the last subject is randomized (ie, all subjects have completed the EOS Visit).

If the study is to be terminated early for reason of futility or efficacy based on interim analysis results, the following definitions would apply to subject follow-up:

- If the study is terminated early for futility, the end of the clinical study is defined as the latest date that a randomized subject has a study visit.
- If the study is terminated early for efficacy, enrollment will cease upon the announcement of the decision to stop the study. In this case, the end of the clinical study is defined as the date the last subject randomized has completed the EOS Visit.

Refer to Section 10.3.6 for details regarding the 3 planned interim analyses and Section 4.3.4 for procedures for subject follow-up.

3.7 Study Oversight

3.7.1 Independent Data Monitoring Committee

An unblinded IDMC will monitor the safe conduct of the study. An IDMC charter outlines the roles and responsibilities of the committee and guides its operations. The IDMC consists of qualified scientists who are not investigators in the study and not otherwise associated with CSLB.

The responsibilities of the IDMC will include the following:

- Review the safety data at planned intervals and identify if significant safety concerns arise during the study.
- Provide recommendations to the Executive Committee chairperson and CSLB regarding study conduct matters that affect safety.
- Request an interim safety review whenever it ascertains one is warranted.
- If warranted due to safety concerns, recommend modifications to study conduct or early study termination.
- Review efficacy and safety data as part of prespecified interim analyses for futility and efficacy, and make recommendations regarding study progression or termination (Section 10.3.6).
- Monitor for the potential risk of an immune response to CSL112 and apoA-I and make recommendations regarding the number of samples to be assayed.

Additionally during the course of study conduct, the IDMC will review unblinded laboratory data to assess safety with respect to hepatic and renal function when the first 20% of enrolled

subjects have completed Visit 6 (Day 29) (Section 10.3.6). In addition, the IDMC will review renal function for those subjects dosed within 12 to < 48 hours after contrast administration. The IDMC can determine whether the requirement for local and / or central laboratory assessments of hepatic and / or renal function before subsequent infusions can be discontinued (ie, blood sampling and review of results can stop (see Schedule of Assessment). If the IDMC so recommends, study investigators will be notified by the Executive Committee Chairperson as to which of these routine laboratory assessments are no longer required, and whether eligibility for all subsequent infusions may be based on clinical assessment (ie, starting with infusion 2 [Visit 3]).

The IDMC will also monitor unblinded (ie, non-aggregated) suspected MACE endpoint events and other safety data to ensure the safety of subjects in the study.

3.7.2 Executive Committee

A blinded Executive Committee will provide clinical guidance on study design, implementation, conduct, and interpretation of results. The Executive Committee will comprise designated representatives from among the principal investigators, other recognized thought leaders in the field of ACS, lipidology, and biostatistics, as well as sponsor representatives. The Executive Committee is described in further detail in its charter.

A subgroup of the Executive Committee will provide academic leadership on study publications. The Publications Committee will be described in further detail in the Executive Committee charter.

3.7.3 Steering Committee

A blinded Steering Committee will be formed consisting of members who are lead investigators from each country / region. The Steering Committee will advise and assist the Executive Committee with regard to the scientific and operational aspects of the study. Details of the composition, roles, and responsibilities of the Steering Committee are documented in its charter.

3.7.4 Clinical Events Committee

An independent Clinical Events Committee (CEC) will review and adjudicate each suspected CV event endpoint while blinded to treatment assignments. Suspected CV event endpoints include all-cause mortality, CV death, all MI, all stroke, and hospitalizations for coronary, cerebral, or peripheral ischemia (including coronary revascularization). The CEC will also review and adjudicate the occurrence of potential hepatic injury, including results from

hepatic laboratory tests and hepatic injury assessments, and new or worsening heart failure (HF), in a blinded fashion. A common group of qualified scientists and physicians will prepare the definitions of endpoints and instructions for interpretation based on available guidance. The CEC is described in further detail in its charter.

3.8 Study Stopping Criteria

At any time, the IDMC may recommend study termination due to safety concerns (Section 3.7.1). Three interim analyses are planned to evaluate the available efficacy data; the IDMC will review unblinded data from these planned interim analyses and may recommend study termination due to futility or strong evidence of efficacy (refer to Section 10.3.6). The IDMC recommendation will be relayed to the Executive Committee chairperson, and then communicated to the CSLB Head of Clinical Development.

4 Selection and Withdrawal of Subjects

4.1 Eligibility Criteria

The study population will be selected on the basis of the inclusion and exclusion criteria described in the following sections. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Subject eligibility should be reviewed and documented by a medically qualified member of the investigator's study team before subjects are included in the study. Infusion 1 must be administered in the timeframe as detailed in Section 4.2.1.

4.1.1 Inclusion Criteria

To be enrolled into the study, subjects must meet all of the following inclusion criteria:

1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements.
2. Male or female at least 18 years of age at the time of providing written informed consent.
3. Evidence of myocardial necrosis in a clinical setting consistent with type 1 (spontaneous) MI (STEMI or NSTEMI) caused by atherothrombotic coronary artery disease (4th Universal Definition of MI [Thygesen et al, 2019]) as defined by the following:
   a. Detection of a rise and / or fall in cardiac troponin I or T with at least 1 value above the 99th percentile upper reference limit.

      AND

b. Any 1 or more of the following:

i. Symptoms of acute myocardial ischemia (ie, resulting from a primary coronary artery event).

ii. New (or presumably new) significant ST/T wave changes or left bundle branch block.

iii. Development of pathological Q waves on electrocardiogram.

iv. Imaging evidence of new loss of viable myocardium or regional wall motion abnormality in a pattern consistent with an ischemic etiology.

v. Identification of intracoronary thrombus by angiography.

Note: Electrocardiograms obtained as part of standard of care can be used to support or confirm the index MI.

4. No suspicion of AKI at least 12 hours after IV contrast agent administration (subjects who have undergone angiography) or after FMC for the index MI (subjects who have not undergone angiography). There must be documented evidence of stable renal function defined as no more than an increase in serum creatinine < 0.3 mg/dL (27 μmol/L) from pre-contrast serum creatinine value.
5. Evidence of multivessel coronary artery disease defined as meeting 1 or more of the following criteria:

a. At least 50% stenosis of the left main coronary artery or at least 2 epicardial coronary artery territories (left anterior descending, left circumflex, right coronary artery) on catheterization performed during the index hospitalization.

b. Prior cardiac catheterization documenting at least 50% stenosis of the left main coronary artery or at least 2 epicardial coronary artery territories (left anterior descending, left circumflex, right coronary artery).

c. Prior PCI and evidence of at least 50% stenosis of at least 1 epicardial coronary artery territory different from prior revascularized artery territory.

d. Prior multivessel coronary artery bypass grafting.

6. Presence of established cardiovascular risk factor(s), defined as:

a. Diabetes mellitus on pharmacotherapy.
OR
b. 2 or more of the following:

i. Age ≥ 65 years.

ii. Prior history of MI.

iii. Peripheral arterial disease defined as meeting at least 1 of the following criteria:

1. Current intermittent claudication or resting limb ischemia AND an ankle brachial index ≤ 0.90.

2. History of peripheral revascularization (surgical or percutaneous).

3. History of limb amputation due to peripheral arterial disease.

4. Angiographic evidence (using computed tomographic angiography, magnetic resonance angiography, or invasive angiography) of a peripheral artery stenosis ≥ 50%.

7. Female subjects must be postmenopausal or with a negative urine pregnancy test prior to randomization. If the urine test cannot be confirmed as negative, a serum pregnancy test will be required. This pregnancy test must be negative for the subject to be eligible.

a. Postmenopausal status is defined as subjects over the age of 60 years, subjects aged 45 to 60 years (inclusive) with amenorrhea for at least 1 year with documented evidence of follicle-stimulating hormone level > 30 IU/L, or subjects who are surgically sterile for at least 3 months before randomization. If the follicle-stimulating hormone value is not available prior to randomization, a urine pregnancy test is required.

b. Females of childbearing potential must be willing to use an acceptable method of contraception to avoid pregnancy while receiving treatment with CSL112 (ie, during the Active Treatment Period) and for 30 days after receipt of the last dose of investigational product; and, if currently breastfeeding a child, willing to cease breastfeeding.

NOTE: Acceptable methods of contraception are:

i. Abstinence, where abstinence is the preferred and usual lifestyle of the subject, including refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable definitions of abstinence.

ii. Surgical sterilization (more than 3 months before randomization) of subject or subject's partner.

iii. Use of intrauterine device (placed more than 3 months before randomization).

iv. Injectable combined hormonal or contraceptive medication implant alone.

v. Injectable single hormone, oral hormonal contraceptive (eg, combined or progesterone only), contraceptive medication patch, or estrogen/progestin vaginal ring plus an acceptable barrier method as outlined below.

Acceptable barrier methods include: female or male condoms, with spermicidal foam or spermicidal jelly, or diaphragm, with spermicidal foam or spermicidal jelly, all of which must be used with an additional method of contraception outlined above. Female condom and male condom should not be used together.

8. Investigator believes that the subject is willing and able to adhere to all protocol requirements.
9. Willing to not participate in another investigational study until completion of their final study visit.

4.1.2 Exclusion Criteria

Subjects must not be enrolled into the study if they meet any of the following exclusion criteria:

1. Ongoing hemodynamic instability defined as any of the following:
   a. A history of New York Heart Association Class III or IV HF within the last year.
   b. Killip Class III or IV.
   c. Sustained and / or symptomatic hypotension (systolic blood pressure < 90 mmHg).
   d. Known left ventricular ejection fraction < 30%.
2. Evidence of hepatobiliary disease as indicated by any 1 or more of the following at screening:
   a. Current active hepatic dysfunction or active biliary obstruction.
   b. Chronic or prior history of cirrhosis or of infectious / inflammatory hepatitis.

Note: If a subject has a medical history of recovered hepatitis A, B, or C without evidence of cirrhosis, he / she could be considered for inclusion if there is documented evidence that there is no active infection (ie, antigen negative).

c. ALT > 3 × upper limit of normal (ULN) or total bilirubin > 2 × ULN at time of randomization. Subjects with a known or suspected history of Gilbert's syndrome are not eligible for study participation if their direct bilirubin is > 2 × ULN.

3. Evidence of severe chronic kidney disease with an estimated glomerular filtration rate of < 30 mL/min/1.73 m^2 (as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation) [Levey et al, 2009; Stevens et al, 2010] or if subject is receiving dialysis.
4. Plan to undergo scheduled coronary artery bypass graft surgery as treatment for the index MI.
5. Body weight < 50 kg.
6. Known history of allergies, hypersensitivity, or deficiencies as follows:
   a. Allergy to soy bean or peanuts (Section 7.1)
   b. Known or suspected hypersensitivity to the investigational product, or to any excipients of the investigational product or placebo (albumin) (Section 5.1.1 and Section 5.1.2, respectively).
   c. A known history of IgA deficiency or antibodies to IgA.
7. Other severe comorbid condition, concurrent medication, or other issue that renders the subject unsuitable for participation in the study, including but not limited to:
   a. A comorbid condition with an estimated life expectancy of ≤ 6 months at the time of consent.
   b. Women who are pregnant or breastfeeding at the time of randomization.
   c. Participated in another interventional clinical study within 30 days of consent or has plans to participate in another interventional clinical study at the time of consent.
   d. Known alcohol, drug, or medication abuse within 1 year before consent to this study.
   e. Treatment with anticancer therapy (chemotherapy, immunotherapy, radiotherapy, targeted therapy, or gene therapy) within 3 months before the first administration of investigational product or at any time during the study. Recovery from associated toxicities (eg, hematologic) must be documented in the source document.

NOTE: Use of low-dose chemotherapy for treatment of a condition other than cancer (eg, rheumatic disease) is permissible. Hormonal therapy or anti-hormonal therapy is also allowed; however, a subject's life expectancy must be > 24 months at the time of consent.

f. Previously randomized or participated in this study or previously exposed to CSL112.

g. Mental condition rendering the subject (or the subject's legally acceptable representative[s]) unable to understand the nature, scope, and possible consequences of the study.

h. Subjects who are incarcerated, including prisoners or subjects compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

i. Inability or unwillingness to comply with all follow-up through end of the study, and / or unwilling to allow review of medical records in accordance with local regulatory requirements at time of consent.

j. Investigator determines that the subject is not suitable for study participation for any other reason.

8. Involved in the planning and / or conduct of the study (applies to CSLB staff, staff at the study site, and third-party vendors).

4.2 Dosing Eligibility

4.2.1 Infusion 1

For all randomized subjects, before administration of infusion 1 of investigational product, each subject must be deemed clinically stable, must meet the renal and hepatic eligibility criteria, and be dosed within 5 days of FMC. In addition:

- For subjects treated medically with or without thrombolytic agents, infusion 1 of investigational product must occur no earlier than 12 hours after FMC.
- For subjects undergoing angiography or PCI, with or without stent placement, infusion 1 of investigational product must occur no earlier than 12 hours after IV contrast administration.

The first infusion should occur before hospital discharge or on the day of discharge. If discharge occurs on a weekend, infusion 1 of investigational product can be administered on the next business day as long as timing is still within 5 days of FMC.

All tests and procedures that are required to determine subject eligibility (ie, screening and randomization) must be performed with enough time to administer the investigational product within the specified timeframe. If angiography is planned for treatment of the index MI, randomization must occur after the procedure has been performed and stability of serum creatinine confirmed at least 12 hours after IV contrast administration. Screening and randomization may occur on the same day (Day 1) provided laboratory results are available for review by the investigator and eligibility criteria have been met for ALT, total bilirubin, and serum creatinine.

Hepatic function (ALT and total bilirubin) must be within acceptable limits and stability of renal function (serum creatinine) must be confirmed by the investigator before administration of infusion 1 of investigational product (Sections 4.2.1.1 and 4.2.1.2, respectively). According to the following criteria, local laboratory values at screening (Visit 1) will be used to determine eligibility for inclusion into the study and eligibility for infusion 1 of investigational product. These local laboratory values will also be considered "baseline" for determining subsequent dosing eligibility.

Local laboratory values obtained as part of standard of care testing for the index AMI event and before obtaining written informed consent may be used to determine study entry and infusion 1 eligibility. However, if results (for ALT, total bilirubin, and / or serum creatinine) are not available, then a blood sample must be obtained for the local laboratory testing. A single blood draw may be performed to collect samples for local and central laboratory testing; a blood sample must be sent to the central laboratory at baseline for study analysis purposes.

4.2.1.1 Key Hepatic Laboratory Requirements before Infusion 1

For the assessment of hepatic function before infusion 1, the following criteria must be met:

- If the screening ALT value (absolute level) is ≤ 3 x ULN and total bilirubin value is ≤ 2 x ULN, then the subject is eligible for dosing.
- If the subject has a known or suspected history of Gilbert's syndrome, a direct bilirubin value must be obtained for the assessment. If the screening direct bilirubin value is ≤ 2 x ULN, then the subject is eligible for dosing. The condition is to be recorded in the targeted medical history electronic case report form (eCRF).

If multiple local laboratory tests are obtained, the ALT or total bilirubin value closest in time before the planned randomization should be used to determine hepatic function eligibility.

4.2.1.2 Key Renal Laboratory Requirements before Infusion 1

There should be no evidence of severe chronic kidney disease; the eGFR must be ≥ 30 mL/min/1.73 m^2 (as calculated by the CKD epidemiology collaboration (CKD-EPI] equation) [Levey et al, 2009; Stevens et al, 2010] and the result is to be reviewed by the investigator before infusion 1 (exclusion criterion 3).

For subjects who have not undergone angiography, a serum creatinine value obtained (collected as part of standard of care or for study purposes by local laboratory) at least 12 hours after FMC for the index event must be reviewed by the investigator to assess renal function. The subject must be considered clinically stable and have hemodynamic stability after the index event for study and dosing eligibility.

For subjects who have undergone angiography and, therefore, have received IV contrast agent, the values for serum creatinine should be obtained before and at least 12 hours after IV contrast administration (ie, screening value). There must be documented evidence of stable renal function defined as an increase in serum creatinine < 0.3 mg/dL (27 µmol/L) from pre-contrast serum creatinine value, and there must be no suspicion of AKI. If multiple local laboratory tests are obtained before the administration of contrast agent, the serum creatinine value closest in time prior to IV contrast administration should be used as reference to assess stable renal function. If a pre-contrast serum creatinine value is not available, historical documentation of serum creatinine within ≤ 6 months from screening is acceptable for use as a reference.

- If the screening serum creatinine value meets the criteria indicated above, then the subject is eligible for dosing.
- If the screening serum creatinine value is increased ≥ 0.3 mg/dL (27 µmol/L) from pre-contrast serum creatinine value, then eligibility for the study and infusion 1 must be delayed.
    - A repeat assessment by local laboratory is to be performed once at least 24 hours later to assess renal stability for study and dosing eligibility.
- If the repeat serum creatinine value is increased < 0.3 mg/dL (27 µmol/L) from the pre-contrast serum creatinine value and there is no suspicion of AKI, then the subject is eligible for dosing.
- If the repeat serum creatinine value is increased ≥ 0.3 mg/dL (27 µmol/L) from the pre-contrast serum creatinine value, then the subject is not eligible for dosing (ie, screen failure).

4.2.2 Subsequent Infusions

Eligibility for the subsequent infusions of investigational product will be determined by the investigator based on clinical assessment (eg, assessments of hemodynamic status, directed physical examination if clinically indicated, and AE assessment) and review of local and / or central laboratory values according to the following criteria (Sections 4.2.2.1 and 4.2.2.2). In addition, the investigator should review the results of any available local and central laboratory ALT, total bilirubin and serum creatinine results from specimens drawn before or after the previous infusion before administering a subsequent infusion of the investigational product.

Note: During the course of study conduct, the IDMC will determine whether the requirement for local and / or central laboratory assessments of hepatic and / or renal function before subsequent infusions may be discontinued (ie, blood sampling and review of results can stop). In that case, all subsequent infusions are to be based on clinical assessment (ie, starting with infusion 2 [Visit 3]).

Each infusion of investigational product should be completed as close to the visit windows outlined in the Schedule of Assessments as possible. An infusion may be skipped (ie, 'missed') or delayed at the discretion of the investigator to evaluate and treat an AE before the next infusion. The time window between each infusion may be extended as long as the last infusion of investigational product is given within 30 days of infusion 1 and the minimum window between infusions is at least 5 days.

4.2.2.1 Key Hepatic Laboratory Requirements before Subsequent Infusions

For assessment of hepatic function before infusion 2, 3, or 4, the following criteria must be met by investigator review of central laboratory values obtained from the previous visits:

- ALT value must be ≤ 3 x ULN and total bilirubin value must be ≤ 2 x ULN for dosing eligibility.
- If the ALT value is > 3 x ULN and total bilirubin value is > 2 x ULN, or if the ALT value is > 5 x ULN then infusion must be delayed.
    - A repeat assessment by local laboratory should be performed once at least 24 hours later to assess hepatic stability and dosing eligibility. Additionally, a blood sample must be sent to the central laboratory for study analysis purposes.

- If the ALT value is > 3 x ULN and ≤ 5 x ULN, or the total bilirubin value is > 2 x ULN, the investigator should perform a clinical assessment using all available data (including assessment of symptoms consistent with liver dysfunction, including right upper quadrant abdominal pain, anorexia, etc.), which may include a repeat laboratory assessment.
  - If the elevation in ALT or total bilirubin is not related to the investigational product and an alternate nonserious etiology is known, the infusion may be administered at the discretion of the investigator.
  - If the repeat ALT value is > 3 x ULN and total bilirubin value is > 2 x ULN, or if the repeat ALT value is > 5 x ULN, then subject should be discontinued from further dosing.

If clinically significant abnormal laboratory test results are identified after investigational product infusion, the test(s) should be repeated until laboratory values return to normal and / or baseline for hepatic function, as per Section 8.1.3.1.1.2, and are reported as AEs as per Section 9.

4.2.2.2 Key Renal Laboratory Requirements before Subsequent Infusions

Before infusion 2, for subjects who received infusion 1 of investigational product > 12 hours and < 48 hours after IV contrast administration, a local laboratory serum creatinine value should be obtained before the infusion for comparison with the local laboratory baseline value and reviewed by the investigator. A blood sample for local laboratory testing to assess dosing eligibility for infusion 2 should not occur earlier than 72 hours following infusion 1.

- If the serum creatinine value is increased < 0.3 mg/dL (27 µmol/L) from the baseline serum creatinine value, then the subject is eligible for dosing.
- If the serum creatinine value is increased between 0.3 and 0.5 mg/dL (27 µmol/L and 44 µmol/L) from the baseline serum creatinine value and it may be attributable to changes in concomitant medications with potential renal effect or other clinical factors (eg, IV fluid discontinued), or falls within range of variability previously observed for the subject as per investigator's discretion and there is no suspicion of AKI, then the subject is eligible for dosing. A repeat creatinine assessment should be performed prior to the next infusion / visit. If variation cannot be attributable to clinical factors as listed above, the infusion should be delayed and repeat assessment of serum creatinine is performed.
- If the serum creatinine value is increased > 0.5 mg/dL (44 µmol/L) from the baseline serum creatinine value, then dosing of infusion 2 must be delayed.

  - A repeat assessment by local laboratory should be performed once at least 24 hours later to assess renal stability for study and dosing eligibility. Additionally, a blood sample must be sent to the central laboratory for study analysis purposes.
- If the repeat serum creatinine value is increased > 0.5 mg/dL (44 µmol/L) from the baseline serum creatinine value (ie, the elevation is confirmed), then the infusion and subsequent infusions must be discontinued.

If clinically significant abnormal laboratory test results are identified after investigational product infusion, the test(s) should be repeated until laboratory values return to normal and / or baseline for renal function, and are reported as AEs per Section 9.

Before infusion 2, for subjects who received infusion 1 of investigational product ≥ 48 hours after FMC or IV contrast administration, eligibility for dosing will be determined by the investigator based on clinical assessment (eg, assessments of hemodynamic status, directed physical exam if clinically indicated, and AE assessment) with support of local and central laboratory serum creatinine values at baseline.

Before infusions 3 and 4, all subjects must meet the following criteria based on a review of central laboratory values from the previous visits (infusions 2 and 3, respectively) compared with the central laboratory baseline value:

- If the serum creatinine value is increased < 0.3 mg/dL (27 µmol/L) from the baseline serum creatinine value, then the subject is eligible for dosing.
- If the serum creatinine value is increased between 0.3 and 0.5 mg/dL (27 µmol/L and 44 µmol/L) from the baseline serum creatinine value and it may be attributable to changes in concomitant medications with potential renal effect or other clinical factors (eg, IV fluid discontinued), or falls within range of variability previously observed for the subject as per investigator's discretion and there is no suspicion of AKI, then the subject is eligible for dosing. A repeat creatinine assessment should be performed prior to the next infusion / visit. If variation cannot be attributable to clinical factors as listed above, the infusion should be delayed and repeat assessment of serum creatinine should be performed.
- If the serum creatinine value is increased > 0.5 mg/dL (44 µmol/L) from the baseline serum creatinine value, then dosing of the infusion must be delayed.
  - A repeat assessment by local laboratory must be performed once at least 24 hours later to assess renal stability for study and dosing eligibility. Additionally, a blood sample must be sent to the central laboratory for study analysis purposes.

- If the repeat serum creatinine value is increased > 0.5 mg/dL (44 µmol/L) from the baseline serum creatinine value, then the infusion and all subsequent infusions should be discontinued.

If clinically significant abnormal laboratory test results are identified after investigational product infusion, the test(s) should be repeated until laboratory values return to normal and / or baseline for renal function, and are reported as AEs as per Section 9.

4.2.3 Infusion Delay

Each infusion of investigational product should be completed as close to the visit windows outlined in the Schedule of Assessments as possible. An infusion may be skipped (ie, 'missed') or delayed at the discretion of the investigator to evaluate and treat an AE before the next infusion. The time window between each infusion may be extended as long as the last infusion of investigational product is given within 30 days of infusion 1 and the minimum window between infusions is at least 5 days.

Refer to the study reference manuals for detailed instructions for how to address study procedures performed in the Active Treatment Period and for detailed instructions for skipped (ie, 'missed') or delayed infusion.

4.3 Discontinuation of Treatment and / or Subject Withdrawal from the Study

Subjects may withdraw from treatment at any time but will continue in follow-up: every subject, including those who prematurely stop taking investigational product, will be followed for vital status and MACE endpoint assessments and complete study procedures as specified in the protocol unless they explicitly withdraw consent from follow-up (Section 4.3.3). The requirements for handling early discontinuations from investigational product are described below. Details of the requirements for subject follow-up are provided in Section 4.3.4. All efforts should be made to confirm vital status for all subjects up to the end of his / her follow-up.

4.3.1 Early Discontinuation of Investigational Product

Subjects may request at any time that further investigational product administration be discontinued, or it may be discontinued at any time at the discretion of the investigator or CSLB for safety, behavioral, or administrative reasons (eg, due to an AE, protocol deviation, or study termination). In accordance with International Council for Harmonisation (ICH)

principles of Good Clinical Practice (GCP), the investigator always has the option to advise a subject to stop further administration of investigational product if the subject's safety or well-being is compromised by the continued administration of investigational product. Concern for the interests of the subject must always prevail over the interests of the study.

If a subject permanently discontinues treatment with investigational product (regardless of the reason) before the end of the planned Active Treatment Period, the subject will undergo an investigational product Early Termination Visit (Visit 6) and continue safety and MACE endpoint follow-up according to the Schedule of Assessments and Section 4.3.4. If the discontinuation occurs at a scheduled visit, the assessments and procedures for the investigational product Early Termination Visit (Visit 6, Schedule of Assessments) should be completed instead of that visit.

If a subject discontinues investigational product (regardless of the reason) between scheduled visits, the subject should be brought into the clinic as soon as possible to complete the investigational product Early Termination Visit / Visit 6 assessments. All subjects should continue follow-up visits for MACE endpoint assessment (Section 4.3.4).

In all cases, reasons for discontinuation of investigational product and the date of last dose will be recorded.

4.3.2 Possible Reasons for Discontinuation of Investigational Product

Possible reasons for subject discontinuation from investigational product include, but are not limited to, the following:

- Adverse event resulting in discontinuation.
- Subject becomes pregnant during the study.
- Need for chronic use of a prohibited concomitant medication, ie, chemotherapy or other investigational product (Section 7.3).
- Decision by subject or proxy.
- Sponsor terminated study.
- Investigative site closed and subject was unable to transfer to another investigative site.

4.3.3 Subject Withdrawal from the Study

Subjects who no longer wish to attend study visits in person will be asked to be contacted for follow-up by telephone or other methods identified below to assess MACE endpoints and vital status. Similarly, subjects who withdraw consent will be asked if they can be contacted at the end of the study to determine vital status, at a minimum. This change to follow-up from in-clinic visits to by telephone or other methods does not constitute subject withdrawal from the study.

Subject withdrawal from the study is defined as the subject's withdrawal of consent from further participation in the study, including any contact by the study site personnel to determine the MACE endpoints and vital status of the subject. Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or CSLB for safety, behavioral, or administrative reasons (eg, due to an AE, protocol violation, subject noncompliance, and study termination). In accordance with ICH principles of GCP, the investigator always has the option to advise a subject to withdraw from the study if the subject's safety or well-being is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study. If a subject is withdrawn from the study by the investigator or further participation is declined by the subject, they will continue to have access to medical care and will be treated as per routine medical practice.

When a subject is contemplating withdrawal from the study, the investigator (in addition to the coordinator) should discuss with the subject the importance of further follow-up and how further follow-up information can be obtained through telephone contact, registered mail contact, contact through referring physician(s), family or friends, or utilization of publically available information. This latter source is the only available option for subjects who withdraw consent. All efforts should be made to confirm vital status at minimum.

Information regarding study outcomes or vital status will be collected if it is available in the public domain, and if it is permitted by local and national law, according to the specific provision included in the signed informed consent. Alternative permitted options to obtain study outcomes and vital status (eg, healthcare providers and / or relatives) will be summarized on a checklist to be provided to all sites participating in the study separate from the protocol; these permitted options are also subject to local and national law. For any subject who withdraws consent for contact by the study site personnel, the reason for withdrawal of consent will be recorded in the eCRF; the investigator will document / sign the

checklist, and describe the discussion with the subject regarding each of the contact methods that were offered. The discussion must be documented.

Withdrawal from the study as a result of an AE and any therapeutic measures that are taken shall be at the discretion of the investigator. If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the investigator, or until the subject is deemed by the investigator to be lost to follow-up.

If the subject withdraws from the study, CSLB will retain and continue to use any data collected before such withdrawal of consent, in accordance with prevailing regulatory guidance.

4.3.4 Procedures for Subject Follow-up

Every effort should be made to educate the subjects on the importance of remaining in the study and attending scheduled study visits up to the end of clinical study, including those required after early discontinuation of investigational product.

All subjects who either complete the Active Treatment Period or who prematurely discontinue investigational product are required to undergo the Visit 6 / Early Termination (Day 29 clinical assessments according to the Schedule of Assessments).

If a subject prematurely discontinues investigational product and is unwilling or unable to attend visits during the Active Treatment Period in-person according to the visit schedule, he / she will be contacted by telephone or other methods to assess study outcomes and vital status. The only exception to this requisite is for subjects who withdraw consent for any form of contact (Section 4.3.3).

Refer to Section 10.3.6 for early study termination rules for futility and efficacy based on the 3 planned interim analyses, respectively. If the study is terminated early for futility, subjects still in the Active Treatment Period should not receive further investigational product and should return to the site for the Early Termination Visit (Visit 6 [Day 29]); subjects in the Follow-up Period should return for their EOS Visit as defined in Section 3.6. If the study is terminated early for efficacy, enrollment will cease upon the announcement of the decision to stop the study.

Other subject follow-up options to collect MACE endpoints and vital status should be pursued according to local laws and regulations. If 1 of these alternate methods to collect

MACE endpoints and vital status is acceptable to the subject, then the subject will be deemed not to have withdrawn consent for follow-up.

Study completion is defined in Section 3.6.

4.3.5 Subjects Potentially Lost to Follow-up

Investigators should make every effort to contact subjects who are potentially lost to follow-up, including pursuing any alternative contact methods permitted by local regulations or agreed upon by the subject. As permitted by local regulations, a third party may be used to locate alternative subject contact information in the public domain that will be provided to the investigator. The following procedures should be performed before a subject will be deemed lost to follow-up at the end of the study:

1. At least 3 documented subject contact attempts should be made (eg, in-person visit, phone, mail, email).
2. If the subject cannot be directly contacted, utilize all contact information provided when the subject signed consent (next of kin, "referring (non-study) physician", etc.).
3. If all contact attempts are unsuccessful, available sources such as electronic medical records and death registries should be reviewed on an ongoing basis until EOS to attempt to locate the subject, as permitted according to local and national laws.
4. A patient locator service should be utilized (as allowed by local laws).
5. These subject contact procedures should be followed by the sites, who will be encouraged to continue their attempts to locate the subject or next of kin up until the database lock before designating a subject lost to follow-up.

4.3.6 Replacement Policy

Subjects withdrawn from the study will not be replaced.

5 Study Interventions

5.1 Description of Investigational Product(s)

5.1.1 CSL112

The study product, CSL112, will be manufactured by CSLB in accordance with Good Manufacturing Practice (GMP) guidelines and local regulatory requirements.

The active component of CSL112 is apoA-I, which is purified from human plasma. Apolipoprotein A-I is formulated with PC and stabilized with sucrose and cholate as excipients. CSL112 will be provided to the site as a sterile, slightly yellow, lyophilized powder containing 2 g total protein in a 100-mL glass bottle with a rubber stopper and an aluminum cap. Before use, each bottle of CSL112 is reconstituted with 50 mL of water for injection, yielding approximately 57 mL of ready-for-use product. For the 6 g CSL112 dose to be used in this study, 3 bottles will be reconstituted for an approximate total of 170 mL of product. Once reconstituted, CSL112 is a pale yellow solution with foaming characteristics.

Further details regarding preparation of CSL112 are specified in the Investigator Brochure and site investigational medicinal product manual (ie, Site IMP Manual).

5.1.2 Placebo

The placebo product will be manufactured by CSLB in accordance with Good Manufacturing Practice guidelines and local regulatory requirements.

The placebo product will be CCI [redacted] in water (CCI for IV infusion. An equivalent amount of placebo (approximately 170 mL) to CSL112 will be intravenously infused in a vein (peripheral or central) over 2 hours. Placebo product will be provided to the site as 50 mL vial of a registered 25% albumin solution. The placebo solution will comprise CCI [redacted] CCI to yield a 4.4% albumin solution. Further details regarding the preparation of the placebo are specified in the Site IMP Manual.

5.2 Packaging, Labeling, Supply and Storage

5.2.1 Packaging and Labeling

CSL112 and placebo product will be packaged and labeled according to current ICH GMP and GCP guidelines, and national legal requirements.

Commercially-available, sterile, water for injection and CCI will be purchased by the study sites for use in the preparation of CSL112 and placebo, respectively.

5.2.2 Supply and Storage

CSL112 and placebo will be supplied to the study sites by CSLB or delegates.

CSL112 must be stored under temperature-monitored conditions (+2°C to +30°C, inclusive) in a secure storage area.

Placebo (albumin) must be stored under temperature-monitored conditions (+2 to +8°C, inclusive) in a secured storage area.

CSL112 and placebo **MUST NOT BE FROZEN**, as this may disrupt the protein structure of each product.

CSL112 and placebo must be protected from light during storage. The individual packaging holding the CSL112 and placebo bottles is sufficient for light protection.

Further details regarding specific storage conditions of CSL112 and placebo are specified in the Site IMP Manual.

5.3 Accountability and Destruction

All supplies of investigational product(s) must be accounted for throughout the study. Records for the delivery of investigational product to the study site, the inventory at the study site, the use by each subject, and the destruction or return of investigational product to CSLB must be maintained by the investigator (or delegate). The records will include dates, quantities, and unique code numbers assigned to investigational product and unique code numbers assigned to the subjects.

Information on the destruction of CSL112 or placebo is provided in the Site IMP Manual.

5.4 Other Intervention(s)

Not applicable.

5.5 Dose Modification

Not applicable.

6 Allocation, Dosing and Administration

6.1 Allocation to Treatment

6.1.1 Subject Assignment

After providing written informed consent, the subject will be issued a study-level unique subject identification number via an interactive response technology (IRT) system. The subject identification number will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

6.1.2 Randomization Procedures

Eligible subjects will be randomized in a 1:1 ratio to receive CSL112 or placebo by means of the IRT. A centralized randomization schedule will be used. The randomization schedule will be stratified by subject's index MI type (STEMI vs NSTEMI), whether they are managed with PCI or medically managed for the index MI, and region (North America, Latin America, Western Europe, Central and Eastern Europe, or Asia Pacific). A balanced distribution of STEMI and NSTEMI is desired, and may require implementation of a limit on an index MI type during the conduct of the study. To ensure the study blind is maintained, the IRT external service provider will prepare the study randomization code according to the specifications provided by the CSLB statistician. The external service provider will keep the randomization code on file.

6.1.3 Blinding Procedures

6.1.3.1 Blinding Method

This study is a double-blind study and, therefore the reference placebo product matches the physical characteristics of the investigational product after preparation. Once prepared according to the instructions given in the Site IMP Manual and transferred to IV infusion bags, CSL112 and placebo match in color and foaming characteristics.

Investigational site staff, including the investigator, will be blinded to treatment allocation. Subjects and CSLB staff participating in the conduct of the study will also be blinded to treatment allocation (double-blind). Study site personnel delegated by the investigator will administer the investigational product by IV infusion in a suitable peripheral or central vein.

Unblinded study site personnel delegated by the investigator will prepare the investigational product and the IV infusion bag and infusion set for administration. The unblinded study site personnel will also ensure the contents remain blinded to the subject and the blinded study site personnel who will be conducting safety assessments. Unblinded study site personnel are not to administer the investigational product and will not be involved in conducting or recording any study assessment procedures (ie, in the care of the subject).

Adequate procedures will be in place to ensure the integrity of the blinded data within CSLB and the study sites. **The investigator and other blinded study staff must not review the results of a lipid panel test (specifically the HDL cholesterol level) during the Active Treatment Period as the results may unblind treatment assignment.**

6.1.3.2 Breaking the Blind for an Emergency

The randomization code for individual subjects may be unblinded to a site during the study in emergency situations for reasons of subject safety, if knowing treatment assignment will change subject management. In case of an emergency situation for the reason of subject safety, the investigator should use IRT to identify the treatment allocation for a subject. Whenever possible, the investigator should consult with the study hotline before unblinding the randomization code. The reason for unblinding the randomization code must be fully recorded in the subject's source documents, and the investigator must follow the defined procedures provided in the study reference manuals. The subject's treatment allocation should not be recorded in the subject's source document.

6.1.3.3 Planned Unblinding Procedures

Three unblinded interim analyses and periodic unblinded safety reviews are planned for this study for the purposes of safety monitoring activities and efficacy assessment by the IDMC (Section 10.3.6). With authorization by CSLB, the IRT external service provider will provide the randomization code to the unblinded statistician (external service provider) performing analyses for the IDMC. At the end of the study, CSLB will authorize that the study be unblinded after database lock. The randomization codes will be provided to the study statistician / delegate.

CSLB Global Clinical Safety and Pharmacovigilance personnel may unblind the randomization code from the IRT to facilitate assessment of suspected unexpected serious adverse reactions (SUSAR) experienced by any subject for expedited reporting to regulatory authorities. MACE are exempt from suspected unexpected serious adverse reactions reporting (see Section 9.6.4).

6.2 Dosing and Administration

The investigator (or delegate) will administer the investigational product only to subjects who provide written consent, meet the inclusion criteria and none of the exclusion criteria (Section 4.1) and have confirmed infusion eligibility (Section 4.2), and will follow the administration parameters outlined in Table 1 as well as the procedures described below. Infusion 1 must be administered in the timeframe as detailed in Section 4.2.1. Infusions 2, 3, and 4 may be administered in the hospital or an outpatient setting at least 5 days apart (see Schedule of Assessments).

Table 1 Investigational Product Dosing Characteristics

Administration parameter	CSL112 6 g	Placebo
Route	Intravenous	Intravenous
Anatomical location	Vein (peripheral or central)	Vein (peripheral or central)
Infusion rate	approximately 170 mL over 2 hours	approximately 170 mL over 2 hours

The blinding procedures are described in Section 6.1.3. After preparation, CSL112 and placebo will be identical in physical appearance at administration. Administration of the investigational product should be completed within 6 hours of preparation of the solution. A dedicated IV line should be used for administration of investigational product. Patency of the IV line should be ensured before the start of the infusion. Subjects should be advised to sit down or lie in a semi-supine position while receiving the infusion. Subjects randomized to the placebo group will receive a volume of placebo matched to the corresponding CSL112 infusion volume.

After completion of the infusion, the IV line should be flushed with saline. The end of the saline flush defines the end of infusion.

Study site personnel who are medically qualified to recognize and treat drug hypersensitivity reactions must be available together with medications and equipment to treat such reactions. All possible drug hypersensitivity reactions require follow-up until resolution (Section 9.1.2.1).

6.3 Treatment Compliance

All doses of investigational product will be administered by IV infusion. Each subject will be considered to have received a complete dose of investigational product if they receive at least 80% of investigational product per infusion.

7 Contraindications, Permitted Therapies and Prohibited Therapies

7.1 Contraindications and Precautions to Further Dosing

CSL112 has previously been administered to humans. Potential risks and guidance to the investigator for use of CSL112 are provided in the current version of the Investigator's Brochure. The administration of CSL112 to any subject not meeting the eligibility criteria for this study, or to any subject not enrolled in this study, is prohibited.

There is potential for allergic reactions or hypersensitivity to CSL112 in certain individuals, given the constituents of the product. CSL112 consists of apoA-I purified from human plasma that may contain IgA and PC derived from soy beans. Therefore, investigators should ensure that subjects do not have a positive history of IgA deficiency or antibodies to IgA and that the subjects are not allergic to either soy bean or peanuts (there is a documented risk of cross reactions to soy in known peanut allergy sufferers).

Regarding placebo, the albumin prescribing information contains warnings for allergic and anaphylactic like reactions and notes hypersensitivity reactions under adverse reactions. The reported rate of anaphylaxis cases is very low. In addition, there has been no correlation between increasing strength and anaphylactic reaction. Due to limited data available for dosage, no trend of the association between dose and anaphylactic reaction can be made.

In the event that a subject experiences signs or symptoms of a hypersensitivity reaction requiring hospitalization or urgent intervention, or there is suspected angioedema during infusion of investigational product, the current infusion and all subsequent infusions must be immediately discontinued. The subject must receive immediate medical assessment and indicated supportive management per the institutional standard of care (Section 9.1.2.1).

If a subject experiences a serious adverse event (SAE) of hypersensitivity reaction within 72 h of administration of a dose of investigational product, or there is suspected angioedema during infusion of investigational product, additional doses of investigational product should not be administered.

7.2 Permitted Therapies

Concomitant medication typical of those taken by the intended target population (ie, ACS-related treatments) is permitted throughout the study unless prohibited as described in Section 7.3 and must be recorded as outlined in Section 8.1.1.3.

7.2.1 Evidence-based Medical Therapy

All randomized subjects should receive evidence-based post-MI care according to local standards of care and national practice guidelines (without a local standard, the current guideline from the American College of Cardiology / American Heart Association / European Society of Cardiology [ACC / AHA / ESC] etc. should be utilized). Close adherence to professional society evidence-based medical therapy in ACS will be emphasized during study conduct, including use of appropriate revascularization (PCI) and pharmacological treatments, such as dual anti-platelet therapy (ie, aspirin in combination with a P2Y12

inhibitor, or aspirin in combination with another anti-platelet agent), angiotensin-converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers [ARBs] for patients intolerant to ACE inhibitors), beta-blockers, statin and other lipid lowering medications.

All concomitant treatment for ACS including the dose, route of administration, and frequency must be documented in the eCRF, including variance from evidence-based medical therapy (eg, aspirin, adenosine diphosphate receptor inhibitors, and statins) (Section 8.1.1.3).

7.3 Prohibited Therapies

The following therapies are NOT PERMITTED during the study:

- Treatment with anticancer therapy (chemotherapy, immunotherapy, radiotherapy, targeted therapy, or gene therapy) at any time during the study.

  NOTE: Use of low dose chemotherapy for treatment of a condition other than cancer (eg, rheumatic disease) is permissible (see Section 4.1.2).

- Administration of any other investigational agent within 3 months before the first administration of investigational product or at any time before the subject's completion of the study.

Subjects are not to be enrolled into the study if they received any prohibited therapy within 3 months of screening. If administration of any prohibited therapy becomes necessary during the study for medical reasons, the subject may be discontinued from receiving further infusions of investigational product. The requirements for handling early discontinuations from investigational product are described in Section 4.3.1.

7.4 Lifestyle Restrictions

There are no study-specific dietary or lifestyle restrictions for subjects who participate in the study.

All randomized subjects should receive evidence-based post-MI care according to local standards of care and national practice guidelines (without a local standard, the current guideline from the ACC / AHA / ESC etc. should be utilized). Close adherence to these guidelines for ACS regarding diet and lifestyle restrictions, physical activity and / or cardiac rehabilitation, and tobacco smoking cessation is to be emphasized during study conduct as per site's standard practice and will be assessed at Days 90, 180 and 365.

7.5 Overdose

For this study, overdose is defined as any single dose 50% greater than the total volume of investigational product (Section 5.1.1) or an infusion rate that exceeds 3 mg/kg/min of sucrose. The effects of any potential overdose with CSL112 have not been studied, and therefore infusion rate for the investigational product should be maintained as per Table 1 (Section 6.2). Total duration of the infusion should not be less than 1 hour. Any suspected overdose resulting in an AE that is considered by the investigator to be medically significant must be reported as a SAE (see Section 9.6.3). See Section 9.6.6 for overdose reporting requirements.

8 Study Procedures and Visit Schedule

8.1 Clinical Procedures

The clinical procedures will be performed at time points as detailed in the Schedule of Assessments, and the basics of these procedures are described in the following sections. Refer to the study reference manuals for detailed instructions on how the assessments should be performed.

8.1.1 Demographics and Baseline Characteristic Assessments

The clinical procedures to be conducted during this study related to the evaluation of population demographics and baseline characteristics are provided in Table 2. These assessments are to be performed at time points (including time windows) as detailed in the Schedule of Assessments.

Table 2 Study Procedures: Demographics and Baseline Characteristics

Assessment / Section Reference	Description
Demographics	Year of birth, years of age, sex, race, ethnicity (where permitted).
Medical history and index MI (see Section 8.1.1.1 for additional details)	Targeted medical history including but not limited to: • Known coronary artery disease (including previous MI, coronary artery bypass surgery and / or PCI) • Diabetes mellitus. • Peripheral artery disease. • Heart failure. • Moderate to severe valvular heart disease. • Hypertension. • Cerebrovascular disease. • History of angina pectoris. • Number of angina events in the prior 24 hours to FMC. • Time from symptom onset to FMC. • Tobacco and / or e-cigarette use. • Gilbert's syndrome.
Physical examination (Section 8.1.1.2)	• Directed physical examination per the site's standard practice. • Body weight and height.
Prior / concomitant therapies (Section 8.1.1.3)	• Selective medications (ACS-related) taken prior to the index MI and those used in the treatment of the index MI prior to enrollment will be collected in a targeted fashion by drug and / or class. • All concomitant treatments for ACS including the dose, route of administration, and frequency must be collected and monitored for change through to the EOS as per Section 7.2.1. • All other concomitant medications will be collected through Day 90. • Medications contributing to or used in the treatment of an SAE will be collected through to the EOS.

ACS = acute Coronary Syndrome; EOS = End of Study; MI = myocardial infarction; FMC = first medical contact; PCI = percutaneous coronary intervention; SAE = serious adverse event.

8.1.1.1 Medical and Surgical History

A review of targeted medical and surgical history will be conducted and should include, but not be limited to, history of prior MI, history of diabetes mellitus, and all additional medical history with implications for health (note that severe chronic kidney disease and evidence of

hepatobiliary disease are reasons for exclusion; Section 4.1.2). Historical documentation of Gilbert's syndrome should be recorded in the eCRF.

Other types of information collected may include: FMC at the first presenting hospital, MI diagnosis, index MI hospitalization dates, details on any IV contrast administration received during angiography, location of occlusion, and interventions received for the index event including revascularizations or medications used.

Targeted medical history events that occur before the initial Screening Visit will be recorded in the targeted medical history section of the eCRF and will only be reported as an AE if there is an increase in the frequency or severity of the condition during the study. If, during the study period, a subject presents with an SAE, only relevant preexisting conditions that support the narrative of the event should be retrospectively recorded in the medical history section of the SAE page of the eCRF.

8.1.1.2 Directed Physical Examination, Body Weight, and Height

A brief directed physical examination, which focuses on pulmonary and CV examination, should be performed at screening and must be performed by the investigator or a medically qualified delegate. Height may be obtained at any time during hospitalization for the index MI. Body weight should be obtained as the Screening Visit, Visit 6 (Day 29), Visit 8 (Day 90), Visit 9 (Day 180), and Visit 11 (Day 365). Height and body weight measurements will be used to calculate body mass index.

Any clinically significant changes occurring between screening and Visit 8 (Day 90) will be documented in the eCRF as an AE. Physical examination should also include hypersensitivity findings, if relevant (Section 9.1.2.1)

8.1.1.3 Prior and Concomitant Medication

Selective medications (ie, ACS-related medications) taken by subjects in the 4 weeks before screening, including those administered for the index MI, and taken or administered at any time during the study will be collected through the EOS. All other concomitant medications taken or administered during the study will be collected through the Visit 8 (Day 90), or beyond in the event of an SAE, or AEs considered related to investigational product, leading to discontinuation of investigational product, and / or leading to withdrawal of consent during the study. The identity (ie, generic name), dose, route of administration, frequency, dates started and stopped (or notation of "ongoing"), and reason for use should be recorded. Exceptions to recording medications / therapies are outlined below.

Concomitant medication typical of those taken by the intended target population is permitted throughout the study unless prohibited as described in Section 7.3. Evidence-based medical therapy (eg, dual anti-platelet therapy, adenosine diphosphate receptor inhibitors, ACE inhibitors [or ARBs for patients intolerant to ACE inhibitors], beta-blockers, and statin and other lipid-lowering medications) should be administered as described in Section 7.2.1. Reasons for variance from use of evidence-based medical therapy (eg, aspirin, adenosine diphosphate receptor inhibitors, and statins) should be noted in the eCRF.

If the use of any concomitant treatment (whether medication or non-pharmacologic treatment) becomes necessary for treatment of an AE, the treatment and administration details must be recorded in the eCRF.

All concomitant medications taken or administered resulting in or for the treatment of an SAE, or AEs considered related to investigational product, leading to discontinuation of investigational product and / or leading to withdrawal of consent during the study, will be collected through the end of the study. These details should include (as appropriate) the reason for treatment, name of the treatment, dose, and unit and route of administration.

Exceptions to Concomitant Medications Reporting
It is not required to record information on the following medications / therapies unless they are deemed to the cause of or contributor to the occurrence of an AE / SAE:

- Intravenous fluid.
- Electrolyte or nutritional replacement.
- Anesthetic medications that are inhaled or topical.
- Medications / therapies that are not directly administered to the subject, such as cardioplegic solution or antithrombin used in conjunction with the cardiopulmonary bypass pump.
- Nonsystemic bowel preparation (eg, enema).
- Topical treatments intended for therapy of dermatologic conditions.
- “As needed” (PRN) medications / therapies (eg, sedatives, bowel preparation) (except for antacids, proton-pump inhibitors, and H2-receptor antagonists – typically taken by the intended target population).
- Medications for surgical or nonsurgical procedures (eg, anesthetic, sedative).
- Vaccines.

8.1.2 Efficacy Assessments

MACE is a composite of endpoints as presented in Sections 2.1, 2.2.2, 2.2.4.1, and 2.3.2. An assessment for MACE should be performed at all visits as outlined in the Schedule of Assessments. All untoward medical occurrences that are potential MACE will be reported as endpoints for adjudication (including all-cause death). The event is to be reported in the appropriate eCRF within 24 hours of the investigator becoming aware of the event. Details of the events will be systematically collected on the eCRF, including event-specific details (Section 9.6.4). The CEC will adjudicate each event according to definitions specified in a separate charter. If multiple suspected MACE occurs in the same subject, each event should be entered separately in the appropriate module(s) of the eCRF. Thus, if a subject has an MI and subsequently dies, the appropriate information would be entered in the separate MI and death modules of the eCRF.

Note: MACE that occur after informed consent but prior to randomization do not need to be adjudicated as endpoints and should be reported as AEs or SAEs as appropriate.

Should an investigator report an SAE during the study that is considered by CSLB to be potentially consistent with a study endpoint, CSLB or delegate will request confirmation from the investigator that this event is indeed an SAE and not an endpoint. The investigator should respond immediately (within 24 hours) to these requests in order to minimize the risk that such an event may require expedited safety reporting. Following the request for review of the reported SAE, and should the investigator consider it as a suspected MACE instead, the event must be reported on the endpoint and / or procedure eCRF (eg, revascularization) for adjudication.

Events following adjudication that are deemed not to be endpoints for this study will be classified as AE / SAEs as soon as the adjudication process has been completed, following standard reporting guidelines. In this instance, the start date for SAE reporting purposes will be the day that the CEC determines that the event is negatively adjudicated. The CEC will notify CSLB within 24 hours of determination of a negatively adjudicated event.

Further details to AE, SAE and MACE endpoint reporting are provided in Sections 9.6.1, 9.6.3, and 9.6.4, respectively.

The modified Rankin score should be obtained if a subject has a suspected or confirmed stroke at the time of occurrence. Scoring of the modified Rankin score is defined in Appendix 2.

If a subject experiences a PCI-related MI (Type 4a), the event will be classified by the CEC based on the baseline status of the subject (ie, before PCI). Baseline status will be determined based on a combination of CV-biomarker samples (eg, troponin or CK-MB; obtained via standard of care practice) as well as ischemic symptoms and ECG changes. In the event of a PCI-related MI, at least 2 pre-PCI CV-biomarker values obtained within 72 hours before PCI are to be recorded in the source. For subjects with NSTEMI, at least 1 of the CV biomarker values recorded in the source should be at least 6 hours before the PCI. At least 3 CV-biomarker values taken after the PCI are to be recorded in the source.

8.1.3 Safety Assessments

Safety assessments are provided in Table 3. Timing of safety assessments will be performed as detailed in the Schedule of Assessments. More frequent evaluations may be performed in the case of an AE, if clinically indicated, at the discretion of the investigator. Clinical laboratory test results that are outside the normal reference range and are deemed clinically significant by the investigator are to be recorded as AEs or SAEs. If clinically significant abnormal laboratory test results are identified after investigational product infusion, the test(s) will be repeated until the values return to normal and / or baseline values.

Table 3 Safety Assessments

Assessment / Section Reference	Description
Adverse events (Sections 9.6.1 and 9.6.3, respectively)	• All AEs will be collected through Visit 8 (Day 90). The following types of AE will be collected through the End of Study (ie, Day 365): o AEs considered related to investigational product. o AEs leading to discontinuation of investigational product. o AEs leading to withdrawal of consent during the study. • All SAEs will be collected through the end of the study, regardless of relationship to investigational product.
Vital signs (Section 8.1.3.4)	• Blood pressure (systolic and diastolic) in mmHg. • Pulse rate (beats per minute).
ALT, total bilirubin, creatinine (Section 8.1.3.2.1)	Local laboratory values obtained as part of standard of care testing for the index MI event will be used for assessment of subject eligibility and infusion 1 eligibility.
Hematology (Section 8.1.3.2.2)	Blood samples will be collected for analysis by the central laboratory: • Hemoglobin • Hematocrit • WBC counts • Total platelet count • CBC with differential

Assessment / Section Reference	Description
Serum Biochemistry (Section 8.1.3.2.2)	Blood samples will be collected for analysis by the central laboratory: • Alkaline phosphatase • ALT • AST • Total bilirubin • Direct bilirubin • BUN • Cholesterol[a] • LDL cholesterol[a] • HDL cholesterol[a] • Creatinine • eGFR (calculated) • Triglycerides[a]
Pregnancy test (Section 8.1.3.3)	Blood or urine test for beta-human chorionic gonadotropin, as indicated for women of childbearing potential. Documented contraception method (if relevant).
Parvovirus testing (Section 8.1.3.5)	Nucleic acid testing and serology (parvovirus B19) will be performed for a subset of subjects.
Immunogenicity testing (Section 8.1.3.6)	Immunogenicity testing will be performed using samples from approximately the first 600 subjects (approximately 300 CSL112 and 300 placebo) and results will provided to the IDMC for review.

AE = adverse event; ALT = alanine aminotransferase; apoA-I = apolipoprotein A-I; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein; IDMC = Independent Data Monitoring Committee; LDL = low density lipoprotein; MI = myocardial Infarction; SAE = serious adverse event; ULN = upper limit of normal; WBC = white blood cell.

[a] All lipid panel analytes must be blinded.

8.1.3.1 Adverse Events Monitoring

Incidence, severity, and causality of AEs, including SAEs, will be evaluated according to the criteria specified in Section 9. The period of observation of AEs extends from the time the subject provides signed informed consent through Visit 8 (Day 90) and, for an individual subject, is to be extended to the EOS Visit (Day 365) for the following instances (see Section 9.4):

- AEs considered related to investigational product.
- AEs leading to discontinuation of investigational product.
- AEs leading to withdrawal of consent during the study.

The period of observation of SAEs for an individual subject extends from the time the subject provides signed informed consent through the EOS Visit (Day 365), regardless of the relationship to investigational product, as specified in Section 9.4. Before and at the end of each infusion conducted at the study site, the investigator or a medically qualified delegate

will specifically inquire (via non-leading questioning) about any AEs that might have occurred since the last infusion conducted at the study site. All AEs (and SAEs and AEs of special interest) will be recorded on the AE page of the eCRF page.

Procedures for reporting AEs, adverse events of special interest (AESIs), and SAEs are specified in Section 9.6.1, Section 9.6.2 and Section 9.6.3, respectively.

8.1.3.1.1 Adverse Events of Special Interest

8.1.3.1.1.1 Hypersensitivity

In the event that a subject experiences an SAE of hypersensitivity, or there is suspected angioedema during infusion of investigational product (as defined in Section 9.1.2), the current infusion and all subsequent infusions must be immediately discontinued. The subject must receive immediate medical assessment and indicated supportive management per the institutional standard of care.

- Additional assessments are to be performed as outlined below. A follow-up is required until resolution of the event. The following assessments should be performed: Collect blood samples for complete blood count with differential (Table 3), levels of quantitative immunoglobulins (immunoglobulins G, M, E, and A), and presence of anti-IgA antibodies.
- A blood sample for immunogenicity testing will be taken as close as possible to the event and tested for anti-CSL112 and anti-apoA-I antibodies.
- The subject should be re-queried to confirm the absence of a history of allergy to soy or peanuts.
- Pertinent positives and negatives should also be assessed and documented in the source document and eCRF including but not limited to: rash, swelling, hives, itching, shortness of breath, wheezing, stridor, and involvement of the mucous membranes.
- Relevant physical examination findings should also be documented (eg, maculopapular rash, swelling of the face or oropharynx, wheezing, etc.).

Any hypersensitivity reaction should be recorded as an AE (Section 9.6.1).

8.1.3.1.1.2 Potential Hepatic Injury

If a subject has elevation in ALT > 3 × ULN with a concomitant increase in total bilirubin > 2 × ULN OR an elevation in ALT > 5 × ULN, blood samples should be obtained and sent to the central laboratory within 48 to 72 hours in order to perform the following assessments:

- ALT, aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase, gamma glutamyl transferase, amylase, and lipase.
- Complete blood count with differential.
- C-reactive protein.
- Prothrombin time / international normalized ratio.
- Serology for Hepatitis A, B, C, D, E.
- Cytomegalovirus titers (Immunoglobulin M, Immunoglobulin G).
- Epstein–Barr virus titers (Immunoglobulin M, Immunoglobulin G).
- Quantitative immunoglobulins (Immunoglobulins G, M, E, and A).
- Anti-nuclear antibodies.

If there is suspicion for autoimmune mediated hepatitis, blood samples should be obtained and sent to the central laboratory for:

- Double-stranded DNA.
- Anti-smooth muscle antibodies.
- Anti-mitochondrial antibodies.
- Cytoplasmic autoantibodies.
- Perinuclear anti-neutrophil cytoplasmic antibodies.

A hepatic injury assessment should include a clinical assessment of symptoms consistent with liver dysfunction, including right upper quadrant abdominal pain, anorexia, etc. Diagnostic imaging of the liver, such as liver ultrasound, should be performed if clinically indicated and should be reported in the eCRF if performed.

Further repeat testing for ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, and gamma glutamyl transferase should occur as clinically indicated but at least every 48 to 72 hours until abnormalities improve or stabilize.

Retesting may decrease to once a week or less if abnormalities stabilize, the investigational product has been discontinued, and subject is asymptomatic to resolution. Retesting of other

relevant parameters may be performed as clinically indicated. Local laboratory assessments may be used for this repeat testing. Consultation with a specialist should be considered if indicated.

The condition resulting in elevations in AST or ALT > 3 × ULN with concomitant elevation in total bilirubin > 2 × ULN, or an elevation in ALT > 5 × ULN should be reported as an AE or SAE as appropriate as per Section 9.6.2.2.

8.1.3.1.1.3 Acute Kidney Injury

If there is an increase from baseline in serum creatinine ≥ 0.3 mg/dL (27 μmol/L), the subject's serum creatinine value must be retested.

8.1.3.2 Clinical Laboratory Testing

During the course of study conduct, the IDMC may recommend whether the requirement for local and / or central laboratory assessments of hepatic and / or renal function before subsequent infusions can be discontinued (ie, blood sampling and review of results can stop). In that case, all subsequent infusions are to be based on clinical assessment (see Sections 3.7.1 and 4.2). The investigator should review the results of any available local and central laboratory ALT, total bilirubin, and serum creatinine results from specimens drawn prior to or subsequent to the previous infusion before administering the investigational product.

During the course of study conduct, the investigator may obtain local laboratory values as part of standard of care testing; however, **the investigator and other blinded study staff must not review the results of a lipid panel test (specifically the HDL cholesterol level) during the Active Treatment Period as the results may unblind treatment assignment**.

8.1.3.2.1 Local Laboratory Testing

Local laboratory values obtained as part of standard of care testing for the index MI event and before obtaining written informed consent may be used to determine hepatic (ALT and total bilirubin) and renal (serum creatinine) function stability for study entry and dosing eligibility of investigational product as per Section 4.2. The use of plasma or whole blood creatinine (instead of serum creatinine) when performed by a certified laboratory using an

approved methodology will be deemed an acceptable alternative to serum creatinine, if serum creatinine testing is not available. If multiple local laboratory tests are obtained:

- The ALT or total bilirubin value closest in time prior to the planned randomization should be used to determine hepatic function eligibility.
- A serum creatinine value obtained at least 12 hours after FMC for the index event to assess clinical stability and determine eligibility for subjects who have not undergone angiography.
- A serum creatinine value closest in time prior to IV contrast administration should be used as reference to assess stable renal function for subjects who have undergone angiography and received IV contrast agent. If a pre-contrast serum creatinine value is not available, historical documentation of serum creatinine within ≤ 6 months from screening is acceptable for use as a reference. The serum creatinine value obtained closest in time to the planned randomization should be used to determine eligibility by comparing it to this historical reference serum creatinine value.

If laboratory testing values from standard of care practices are not available to assess hepatic and renal function eligibility, then a blood sample must be obtained for local laboratory testing. The laboratory values must be confirmed by the investigator for eligibility before administration investigational product. A single blood draw may be performed to collect samples for local and central laboratory testing; a blood sample must be sent to the central laboratory at baseline for study analysis purposes (Section 8.1.3.2.2).

8.1.3.2.2 Central Laboratory Testing

Blood for the clinical laboratory tests presented in Table 3 is to be obtained from the subject as outlined in the Schedule of Assessments. Before infusion 2, 3, and 4, the ALT, total bilirubin and serum creatinine criteria must be met by review of central laboratory (obtained from the previous visits) by the investigator as indicated in Sections 4.2.2.1 and 4.2.2.2. Any additional testing is considered part of standard of care and / or unscheduled visit at the discretion of the investigator to assess subject safety.

Clinical laboratory test results (serum biochemistry and hematology) from the central and / or local laboratory that are outside the normal reference range and are deemed clinically significant by the investigator are to be recorded as AEs (Section 9.6) or SAEs (Section 9.6.3). Refer to Table 3 for specific serum biochemistry and hematology parameters for testing. If clinically significant abnormal laboratory test results are identified after

investigational product infusion, the test(s) will be repeated until the values return to normal and / or baseline. Safety parameters should be repeated if the specimen is hemolyzed.

Investigators must review all laboratory results to assess for clinical significance and to determine if values meet criteria for AEs (Section 9.1.1).

Refer to the Laboratory Manual for details about the collection, storage, handling, and transportation of biological specimens.

8.1.3.3 Pregnancy Test

All female subjects of child-bearing potential will be tested using a urine pregnancy test for beta-human chorionic gonadotropin. Country-specific mandates may require additional pregnancy testing prior to each infusion.

All female subjects of child-bearing potential must have a negative urine pregnancy test. If the urine test cannot be confirmed as negative, a serum pregnancy test will be required. This pregnancy test must be negative for the subject to be eligible (Section 4.1.1).

8.1.3.4 Vital Signs

Vital signs measurement will include blood pressure (systolic and diastolic) and pulse rate according to site's standard practices. Blood pressure and pulse rate will be measured after the subject has rested. Pulse rate will be counted and adjusted per minute or measured with an automatic blood pressure monitor.

8.1.3.5 Parvovirus Testing

Samples will be collected from all randomized subjects at Visit 2 (Day 1; before infusion 1) and Visit 6 (Day 29), and will be stored for up to 1 year after completion of the clinical study report or for the duration permitted by national or local regulations for routine testing or safety surveillance. Nucleic acid testing and serology (parvovirus B19) will be performed using complete samples (at all timepoints indicated in Schedule of Assessments) from approximately 300 randomly selected subjects (approximately 150 CSL112 and 150 placebo) to evaluate changes from baseline (ie, evidence of seroconversion or infection) for parvovirus B19.

8.1.3.6 Immunogenicity Testing

Immunogenicity testing will be performed using blood samples from approximately the first 600 subjects (approximately 300 CSL112 and 300 placebo), and results will provided to the

IDMC for review (Section 3.7.1). If no immunogenicity signal is observed in the CSL112-treated subjects, the IDMC can recommend that no further samples be assayed for immunogenicity. Samples will continue to be collected from all randomized subjects and will be stored for up to 1 year after completion of the clinical study report or for the duration permitted by national or local regulations for routine testing or surveillance as immunogenicity testing is part of evaluation for a serious hypersensitivity reaction.

In the event that a subject experiences an SAE of hypersensitivity, or there is suspected angioedema during infusion of investigational product, the subject's blood samples taken at baseline and at the time of the serious hypersensitivity reaction will be analyzed for the presence of binding antibodies specific to CSL112 and apoA-I.

8.1.4 Other Assessments

8.1.4.1 Quality of Life Questionnaire

The EQ-5D-3L is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The questionnaire, which is designed for self-completion by respondents, is applicable to a wide range of health conditions and treatments [EuroQol Group, 1990]. The questionnaire is to be completed at Visits 1 and 8.

The EQ-5D-3L consists of 2 parts:

- A descriptive profile, comprising the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Subjects rate each dimension based on 3 levels of severity (ie, no problems, some problems, extreme problems).
- A vertical, visual analog scale (VAS), on which the subject rates their overall health from 'Best imaginable health state' to 'Worst imaginable health state'.

8.1.4.2 Lifestyle Adherence Assessment

Adherence to guidelines regarding diet and lifestyle restrictions, physical activity and / or cardiac rehabilitation, and tobacco smoking cessation will be assessed at Visit 8 (Day 90), Visit 9 (Day 180), and the EOS Visit (Day 365) (see Section 7.4).

8.1.5 Pharmacokinetic / Pharmacodynamics Assessments

Blood samples from randomized subjects at selected sites, who provide signed informed consent for PK and PD blood sample collection, will be collected at time points listed in the Schedule of Assessments for determination of the PK parameters of CSL112 through analysis of apoA-I and PC plasma concentrations and PD analyses of lipid biomarkers (cholesterol

efflux), respectively. Sample analysis will be conducted as detailed in the study reference manuals.

8.2 Blood Samples

Detailed information on the estimated volume of blood to be sampled for each assessment and / or by visits will be available in the informed consent form (ICF) and study reference manuals. Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples. Refer to the study reference manuals for details about the collection, storage, handling, and processing of blood samples.

8.3 Retention of Samples for Future Biomedical Research

Retention samples including whole blood will be obtained at time point(s) specified in the Schedule of Assessments for future biomedical research (FBR), including for genomic use, from consenting subjects. Retention samples will be stored and will be destroyed within 10 years after completion of the clinical study report, or for the duration permitted by national or local regulations. Refer to the study reference manuals for further details about the storage and destruction of retention samples.

Research for biomedical testing is to address emergent questions not described elsewhere in the protocol and will only be conducted on a subset of appropriately consented subjects. Research may be done to explore and identify biomarkers that inform the scientific understanding of the disease and / or therapeutic treatment. The overarching goal is to use the information to understand the risk and progression of the disease of interest, and to develop safer, more effective drugs and / or to ensure the correct dose of drug at the correct time. Future biomedical research testing including samples intended for storage and / or future analyses (eg, archival blood sample) will be collected at time point(s) specified in the Schedule of Assessments.

The decision to assess additional biomarkers from an archival blood may be made by the Executive Committee with input from the Steering Committee, and based on the latest available information on the utility of such measurements. These analyses, including genotypic analysis, may be used for future planning and / or exploratory analyses.

8.4 Concomitant Therapies

All drugs and / or procedures currently being administered to a subject at the time of signing informed consent, and which continue to be taken in addition to investigational product

during the study, are regarded as concomitant therapies and must be documented as such in the eCRF. Refer to Sections 7.2 and 8.1.1.3 for detailed instructions.

8.5 Visit Schedule

The timing and frequency of the study visits, including assessment time windows, are presented in the Schedule of Assessments.

8.5.1 Visit 1 (Screening)

All subjects must provide written informed consent before any study-specific assessments or procedures are performed. Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of study eligibility.

Subjects will be assessed for eligibility at screening (Visit 1). Screening / eligibility assessment should occur before or on the day of hospital discharge. Before infusion 1 of investigational product is administered, the subject must be clinically stable and meet all of the inclusion and none of the exclusion criteria (Section 4.1). Hepatic and renal eligibility must be confirmed by the investigator and there must be no suspicion of AKI (Section 4.2.1).

Subjects who complete all of these assessments and who fulfill all eligibility criteria (ie, eligible subjects) will be enrolled into the study. If the subject is not eligible for the study, the subject information and primary reason for screen failure must be entered in the IRT.

Screening and randomization of subjects may occur on the same day (Day 1 of the Active Treatment Period) provided that the minimum time window after FMC for the index event is met. All tests and procedures that are required to be performed to determine subject eligibility (ie, screening and randomization) must be performed with enough time to administer the investigational product within this timeframe. If angiography is planned for treatment of the index MI, randomization must occur after the procedure has been performed and stability of serum creatinine confirmed at least 12 hours after IV contrast administration.

The following procedures will be conducted and documented at the Screening Visit:

- Informed consent.
    - All subjects must provide written informed consent before any study-specific assessments or procedures are performed. Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for

diagnosis or treatment); results from such assessments may be used in the determination of study eligibility.

- Informed consent for FBR (optional).
- Medical and surgical history.
- Prior / concomitant medication review.
- Review of inclusion and exclusion criteria.
- IRT subject registration and randomization (if eligible).
  - If the subject is not eligible for the study, the primary reason for screen failure must be entered in the IRT system.
- Pregnancy test (if applicable).
- Demography (year of birth, years of age, sex, race, and ethnicity).
- Height.
- Vital signs.
- Directed physical examination.
- Body weight.
- Blood sample for local laboratory testing (ALT, total bilirubin, and serum creatinine to confirm infusion eligibility), unless already collected as part of standard of care.
- AE / SAE monitoring.
- EQ-5D-3L questionnaire.

8.5.2 Active Treatment Period

8.5.2.1 Visit 2 (Infusion 1)

Infusion 1 must be administered in the timeframe as detailed in Section 4.2.1.

Before infusion 1 of investigational product, hepatic and renal eligibility based on test results from the local laboratory must be confirmed by the investigator, and there must be no suspicion of AKI (Sections 4.2.1 and 8.5.1).

Before the start of infusion, perform the following assessments:

- Prior / concomitant medication review.
- Vital signs.
- Blood sample for central laboratory testing (biochemistry panel and hematology).

- Blood sample for immunogenicity testing (to be retained in the case of a subject experiencing serious hypersensitivity or suspected angioedema during infusion of investigational product infusion).
- Blood sample for parvovirus testing.
- Blood sample for FBR (if subject consented).
- Blood sample for PK / PD assessment (at selected sites).
- AE / SAE monitoring.

Administer the first IV infusion of investigational product (placebo or CSL112) (Section 6.2).

At the end of the infusion, perform the following assessments:

- AE / SAE monitoring.
- MACE endpoint assessment.
- Blood sample for PK / PD assessment (at selected sites)

8.5.2.2 Visits 3, 4, and 5 (Infusions 2, 3, and 4)

Each infusion of investigational product should be completed as close to the visit windows outlined in the Schedule of Assessments as possible. An infusion may be skipped (ie, 'missed') or delayed at the discretion of the investigator to evaluate and treat an AE before the next infusion. The time window between each infusion may be extended as long as the last infusion of investigational product is given within 30 days of infusion 1 and the minimum window between infusions is at least 5 days.

Refer to the study reference manuals for detailed instructions for how to address study procedures performed in the Active Treatment Period and for detailed instructions for skipped (ie, 'missed') or delayed infusion.

Before infusion 2, dosing eligibility depends on timing of infusion 1 relative to IV contrast administration in the subsets of subjects as follows:

- For subjects who received infusion 1 of investigational product > 12 hours and < 48 hours after IV contrast administration, a local laboratory serum creatinine value must be obtained before the infusion for comparison with the local laboratory baseline value and reviewed by the investigator. A blood sample for local laboratory testing to assess dosing eligibility for infusion 2 should not occur earlier than 72 hours following infusion 1 (refer to Section 4.2.2.2 for dosing eligibility).

- For subjects who received infusion 1 of investigational product ≥ 48 hours after FMC or IV contrast administration, eligibility for dosing will be determined by the investigator based on clinical assessment (eg, assessments of hemodynamic status, directed physical exam if clinically indicated, and AE assessment) with support of local and central laboratory serum creatinine values at baseline (refer to Section 4.2.2.2 for dosing eligibility).

Before infusions 3 and 4, eligibility for dosing will be determined by the investigator based on clinical assessment (eg, assessments of hemodynamic status, directed physical exam if clinically indicated, and AE assessment) with support of available local and central laboratory serum creatinine values at baseline and follow up (refer to Section 4.2.2.2 for dosing eligibility).

Before the start of infusions 2, 3, and 4, perform the following assessments:

- Prior / concomitant medication review.
- Prior laboratory value review (see footnote M in the Schedule of Assessments).
- Vital signs.
- Infusions 2 and 3 only: blood sample for central laboratory testing (biochemistry panel).
- AE / SAE monitoring.
- MACE endpoint assessment.

Administer the IV infusions 2, 3, and 4 of investigational product (placebo or CSL112) (Section 6.2).

At the end of the infusion, perform the following assessments:

- AE / SAE monitoring.
- MACE endpoint assessment.
- Infusion 4 only: blood sample for PK / PD assessment (at selected sites).

8.5.2.3 Visit 6 (End of Active Treatment Period)

- Visit 6 (Day 29) is the end of the Active Treatment Period and should occur approximately 7 (± 2) days after infusion 4 (or last infusion) of investigational product.
- Prior / concomitant medication review.
- Vital signs.
- Body weight.

- Directed physical examination.
- Pregnancy test (if applicable).
- Blood sample for central laboratory testing (biochemistry panel and hematology, immunogenicity, and parvovirus testing).
- AE / SAE monitoring.
- MACE endpoint assessment.
- Blood sample for FBR (if subject consented).

8.5.3 Visits 7, 8, 9, 10, and 11 (Follow-up Period)

Visit 7 and Visit 10 assessments may be conducted either by telephone contact or face-to-face at the study site. Visit 8, 9, and 11 assessments should be conducted face-to-face at the study site.

- Concomitant medication review of all treatments for ACS including the dose, route of administration, and frequency must be collected and monitored for change through to the EOS (Day 365). Note: All other concomitant medications taken or administered during the study will be collected through Visit 8 (Day 90), or beyond in the event of an SAE, or AEs considered related to investigational product, leading to discontinuation of investigational product, and / or leading to withdrawal of consent during the study.
- MACE endpoint assessment (all visits).
- Body weight (Visits 8, 9, and 11).
- Lifestyle adherence assessment (Visits 8, 9, and 11).
- AE monitoring (Visits 7 and 8). Note: AEs considered related to investigational product, leading to discontinuation of investigational product, and / or leading to withdrawal of consent during the study are also to be collected at Visits 9, 10, and EOS.
- AEs related to investigational product / SAE monitoring (all visits).
- EQ-5D-3L assessment (Visit 8).

8.5.4 Early Termination Visit

Subjects who prematurely discontinue infusion(s) of investigational product are to be assessed at Visit 6 / Early Termination Visit as soon as possible after discontinuation of investigational product. Refer to Sections 4.3.1 and 4.3.3 for definition of discontinuation of treatment and / or subject withdrawal from study, respectively, and Sections 4.3.4 and 4.3.5 for follow-up procedures.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

As per the ICH guidelines, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a preexisting condition.
- A clinical event occurring after consent but before investigational product administration.
- Intercurrent illnesses with an onset after administration of investigational product.

Adverse events do not include:

- Events identified at screening that meet exclusion criteria.
- Medical or surgical procedures (the condition that leads to the procedure is the AE).
- Situations where an untoward medical occurrence has not taken place. For example:
  - Planned hospitalizations due to preexisting conditions, which have not worsened.
  - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).
  - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, low dose chemotherapy for a rheumatologic disorder).
  - Overdose of investigational product or any concomitant therapy that does not result in any AE signs or symptoms.

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must be recorded in the eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at screening, unless a further increase / decrease can be considered an exacerbation of a preexisting condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life or outside the measuring range).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE).

9.1.2 Adverse Events of Special Interest

Adverse events of special interest will include hypersensitivity, potential hepatic injury, AKI, and new or worsening of pre-existing HF. Potential hepatic injury and new or worsening of pre-existing HF will be adjudicated by the CEC (Section 3.7.4). At each scheduled study assessment, the investigator or a medically qualified delegate will specifically inquire about any AEs that might have occurred since the last infusion. All AEs will be recorded on the AE page of the eCRF page.

The reporting requirements for AEs of Special Interest are detailed in Section 9.6.2.

9.1.2.1 Hypersensitivity

Hypersensitivity findings may include allergic reactions, bronchospasm / wheezing, generalized rash, swelling, hives, involvement of the mucous membranes, anaphylaxis, etc. Study site personnel who are medically qualified to recognize and treat hypersensitivity reactions must be available together with medications and equipment to treat such reactions.

In the event that a subject experiences signs or symptoms of a hypersensitivity reaction requiring hospitalization or urgent intervention, or there is suspected angioedema during (or within 6 hours following) an infusion of investigational product, the current infusion and all subsequent infusions must be immediately discontinued. The subject must receive immediate medical assessment and indicated supportive management per the institutional standard of care. In the event that a subject experiences an SAE of hypersensitivity, or there is suspected angioedema during infusion of investigational product, assessments should be performed as detailed in Section 8.1.3.1.1.1.

9.1.2.2 Potential Hepatic Injury

Hy's Law is by definition an elevation in ALT or AST > 3 × ULN with a concomitant increase in total bilirubin that is > 2 × ULN without initial findings of cholestasis (elevated alkaline phosphatase > 2 × ULN), and with no other reason found to explain the combination of these increased ALT / AST and total bilirubin findings [FDA Guidance for Industry, 2009]. For the purpose of this study, potential Hy's law cases are defined as an elevation in ALT > 3 × ULN with a concomitant increase in total bilirubin that is > 2 × ULN that is confirmed by repeat assessment, without initial findings of cholestasis (ie, without elevated alkaline phosphatase) and with no other reason to explain the combination of these increased ALT and total bilirubin findings. Note that elevated AST is not being used in the definition for this study because there may be increases in AST that are due to the index MI event. If any subject has elevation in ALT > 3 × ULN with a concomitant elevation in total bilirubin > 2 × ULN OR an elevation in ALT > 5 × ULN, blood samples should be obtained and sent to the central laboratory within 48 to 72 hours in order to perform the assessments detailed in Section 8.1.3.1.1.2. All potential hepatic injury AEs and laboratory values meeting these criteria will be sent to the CEC for adjudication (Section 3.7.4).

9.1.2.3 Acute Kidney Injury

Acute Kidney Injury for this study purpose is defined as any increase from the baseline in serum creatinine of ≥ 0.3 mg/dL (27 µmol/L) during the Active Treatment Period.

Further guidance to reporting AKI as an AE is in Section 9.6.2.3.

9.1.2.4 New or Worsening Heart Failure

New or worsening HF is defined as an event requiring an urgent, unscheduled medical attention, with a primary diagnosis of HF, where the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF. Any suspected new or worsening of HF events will be sent to the CEC for adjudication (Section 3.7.4).

9.1.3 Serious Adverse Event

A SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.

- **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization** – CSLB considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
- **Results in persistent or significant disability or incapacity**.
- **Is a congenital anomaly or birth defect**.
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent 1 of the above outcomes listed as an SAE criterion.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

9.2 Severity of Adverse Events

The severity of each AE (ie, nonserious and serious AEs) is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

AE = adverse event.

Note: Definitions are based on the Clinical Data Interchange Standards Consortium Study Data Tabulation Model Severity Intensity Scale for AE Terminology.

9.3 Causality of Adverse Events

The causal relationship of an AE to investigational product **must always be assessed** by the investigator. All AEs will be classified as either **related** or **not related** to investigational

product. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to investigational product.

The degree of certainty with which an AE is attributed to investigational product or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of investigational product.
- Clinically and / or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor).
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with investigational product, drug withdrawal or reproduced on rechallenge).
- Evidence from the literature.

9.4 Observation Period for Adverse Events

The observation period for AE reporting for an individual subject will start at the time of giving written informed consent for participation in the current study and through Visit 8 (Day 90) and, for an individual subject, is to be extended to the EOS Visit (Day 365) in the following instances: AEs considered related to investigational product, AEs leading to discontinuation of investigational product and AEs leading to withdrawal of consent. The observation period for SAE reporting for an individual subject will start at the time of giving written informed consent and continue through to the EOS.

If an SAE occurs at any time during the study (including after the observation period has finished and there is at least a possible causal relationship to investigational product), the event must be reported to CSLB (see Section 9.6.3).

9.5 Follow-up of Adverse Events

Every effort should be made to follow AEs until resolution or stabilization. Ongoing, nonserious AEs that have not resolved or stabilized will be followed until the subject completes the study. SAEs will be followed until the AE resolves, stabilizes, or the subject is lost to follow-up.

All follow-up information (and attempted follow-up contacts) should be documented in the subject's medical records. Details of the subject's progression to the SAE should also be submitted to CSLB Global Clinical Safety and Pharmacovigilance.

9.6 Adverse Event Reporting

9.6.1 Adverse Events

The investigator (or delegate) will determine whether any AEs have occurred throughout the study as per Section 9.4. AEs will be recorded in the AE module of the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms.

The investigator must follow-up on the course of an AE until resolution or stabilization. If an AE is ongoing after the subject's EOS Visit, the AE will continue to be followed until resolution, stabilization, a new baseline is achieved, or the subject is lost to follow-up, whichever is sooner, or to the end of the study.

If during the study period a subject presents with an SAE, only relevant preexisting condition to support the narrative of the event should be retrospectively recorded. For AE reporting, the study period is defined as that time period from the signature of the ICF through Visit 8 (Day 90) and is to be extended to the end of study for specific instances as outlined in Section 9.4.

9.6.2 Adverse Events of Special Interest

If an AESI is considered serious, the event must be reported to CSLB as described in Section 9.6.3 (Serious Adverse Event Reporting).

9.6.2.1 Hypersensitivity

In the event that a subject experiences signs or symptoms of a hypersensitivity reaction requiring hospitalization or urgent intervention, or there is suspected angioedema during infusion of investigational product, the current infusion and all subsequent infusions must be immediately discontinued. In the event that a subject experiences an SAE of hypersensitivity, or there is suspected angioedema during infusion of investigational product, the event should be reported as an SAE within 24 hours of the investigator awareness of the event as described in Section 9.6.1. Assessments for serious hypersensitivity reactions or suspected angioedema during infusion of investigational product should be performed as described in Section 8.1.3.1.1.1.

9.6.2.2 Potential Hepatic Injury

An elevation in ALT > 3 × ULN with a concomitant increase in total bilirubin that is > 2 × ULN should be reported as an SAE within 24 hours of the investigator awareness of the event as described in Section 9.6.3. An elevation in ALT that is 5 × ULN should be reported as an AESI but is only to be reported as an SAE if it meets SAE criteria (Section 9.1.3). Additional assessments in the event of either laboratory criterion should be performed as described in Section 8.1.3.1.1.2. All potential hepatic injury AEs and laboratory assessments for values meeting these criteria will also be sent to the CEC for adjudication (Section 3.7.4).

9.6.2.3 Acute Kidney Injury

Acute kidney injury for this study purpose is defined as any increase from baseline in serum creatinine value of ≥ 0.3 mg/dL (27 µmol/L) during the Active Treatment Period. In such instances, the serum creatinine value must be retested. As described in Section 9.6.1 the laboratory abnormality or associated condition should be reported as an AE if it is deemed by the investigator as an abnormal, clinically significant finding.

9.6.2.4 New or Worsening Heart Failure

Any suspected new or worsening of HF events will be sent to the CEC for adjudication (Section 3.7.4). This event is considered exempt from SAE reporting as per Section 9.6.4 and is to be reported in the appropriate endpoint eCRF.

9.6.3 Serious Adverse Event Reporting

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the eCRF. If an electronic document is not able to be generated (eg, internet access problem), a handwritten paper SAE report must be completed, which must be signed and dated by the investigator.

All SAEs that occur during the course of the study, whether or not causally related to investigational product, must be entered into the eCRF immediately (within 24 hours of the investigator becoming aware of the event).

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to investigational product that meet 1 or more of the seriousness criteria for AEs must be entered into the eCRF in the same manner as other SAEs and will be included in the clinical study database and reported to CSLB.

Any SAE that occurs after the EOS Visit through study database lock as specified in Section 3.6 that is considered to be causally related to investigational product must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSLB.**

The minimum reporting requirements for reporting of SAEs include:

- Subject identification number.
- Suspected medicinal product and / or procedure.
- Event term.
- Reporting source identification.

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event.

In addition, the investigator must:

- Report all SAEs to the relevant Institutional Review Board (IRB) / Independent Ethics Committee (IEC) as required within the timeframe specified by the IRB / IEC.
- Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for all SAEs is entered in the eCRF.

When submitting SAE reports and any other related reports (eg, discharge summaries) to CSLB, subjects should be identified only by their subject number and study number. The investigator should not include the subject's name, date of birth, or address.

In the case of negative adjudication of an event by CEC, the start date for safety reporting purposes begins when the event has been negatively adjudicated (see Section 9.6.5). The CEC will notify CSLB Safety within 24 hours of a negative adjudication.

The procedure to be followed if an ongoing AE becomes an SAE after the end of the observation period for AEs is described in Section 9.5. Contact details and guidance for reporting SAEs will be provided to study sites before the study starts.

9.6.4 Suspected MACE Reporting

MACE is a composite of the study efficacy endpoints as presented in Sections 2.1, 2.2.2, 2.2.4.1, and 2.3.2, with further description in Section 8.1.2. All untoward medical occurrences that are suspected MACE will be reported as endpoints for CEC adjudication. All suspected MACE will be entered by sites on the AE / SAE eCRF. Sites will also complete the details needed for adjudication on the endpoint eCRF.

Note: MACE that occur after informed consent but prior to randomization do not need to be adjudicated as endpoints and should be reported as AEs or SAEs as appropriate.

Suspected MACE events entered on the SAE / AE eCRF page **will not** be subject to expedited safety reporting by CSLB unless the event is determined by the CEC to not meet study endpoint criteria as defined in the CEC charter (ie, negative adjudication of the potential endpoint; see Section 9.6.5).The suspected MACE are as follows:

- CV death.
- MI.
- Stroke.
- Hospitalizations for coronary, cerebral or peripheral ischemia.

ALL deaths should be reported as an endpoint for adjudication. Non-CV death will be adjudicated by the CEC and should undergo standard SAE reporting in parallel with the CEC adjudication. In cases of death (CV or non-CV), the investigator should supply the CEC and the IEC / IRB (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports). IEC / IRB notification of suspected MACE may be required; therefore sites should follow local ethic guidance for reporting of these events.

New or worsening HF is considered an AESI that will also be adjudicated by the CEC for safety. A serious event of this condition is exempted from expedited safety reporting by CSLB unless it is negatively adjudicated by the CEC (Section 9.6.5).

Potential hepatic injury (defined in Section 9.1.2.2) is considered an AESI that will also be adjudicated by the CEC for safety. Potential hepatic injury events will undergo standard SAE reporting in parallel with the CEC adjudication.

Suspected MACE and new or worsening HF events will be centrally adjudicated by a blinded CEC according to the guidelines specified in a separate charter. All MACE, new or

worsening HF events, or triggered requests for additional information will be reviewed and adjudicated by the CEC without unblinding treatment.

9.6.5 Negative Adjudication

Suspected MACE and new or worsening HF will be evaluated by the CEC. If the reported event is determined to not meet study endpoint criteria as defined in the CEC charter (ie, negative adjudication of the event) and meets serious criteria, or if CV death is adjudicated by the CEC as non-CV death, then the event is to be classified as an SAE by CSLB.

In the case of negative adjudication of an event by the CEC, the start date for safety reporting purposes by CSLB begins when the event has been negatively adjudicated. The CEC will notify CSLB within 24 hours of a negative adjudication.

It is important to note that ALL deaths must be reported as an endpoint and sent for adjudication. Only those suspected MACE of CV death that the CEC deems to be of non-CV cause will be classified by CSLB as an SAE for expedited reporting. CSLB will be notified by the CEC of these non-CV deaths.

9.6.6 Overdose

Any overdose of investigational product that occurs in association with an adverse sign or symptom must be entered into the eCRF as an AE; if the AE meets any seriousness criteria, the event must be reported as an SAE (see Section 9.6.3). An overdose that does not result in any adverse signs or symptoms should not be considered an AE (see Section 9.1.1).

Details (ie, volume, location of infusions) of overdose of investigational product (defined in Section 7.5) must be recorded in the study treatment administration eCRF. Details of overdose of any concomitant therapy should be recorded in the concomitant medication eCRF.

9.6.7 Pregnancy and Breastfeeding

A female subject or female partner of a male subject who becomes pregnant while participating in the study up to and including Visit 7 (Day 60), must notify the investigator immediately. CSLB must be notified within 5 days of the investigator becoming aware of the pregnancy.

If a female subject becomes pregnant, she must discontinue treatment with investigational product, but may continue other study procedures at the discretion of the investigator. The

procedure for discontinuation of a subject will be followed, as described in Section 4.3. Every effort will be made to ensure that the relevant safety assessments for Early Termination Visit 6 are completed (telephone documentation is allowed).

A pregnancy in a subject or in a female partner of a male subject exposed to investigational product should be followed to term to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to CSLB using a Pregnancy Reporting / Outcome Form.

All abnormal pregnancies and neonatal outcomes (eg, spontaneous abortion, stillbirth, neonatal death or congenital anomaly) will meet the criteria for SAE classification. The investigator should follow the procedure for reporting these events as SAEs (Section 9.6.3).

9.7 Institutional Review Board / Independent Ethics Committee Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB / IEC. It is the investigator's responsibility to comply with the requirements for IRB / IEC notification. CSLB will provide investigators with all details of all SAEs reported to regulatory authorities.

10 Statistics

10.1 Sample Size

10.1.1 Estimation

The study is designed as a superiority study. The sample size calculation is based upon the hypothesis that compared with placebo, CSL112 will have a 20% relative risk reduction (hazard ratio = 0.80) in the primary endpoint over 90 days of follow-up after randomization (ie, all subjects will be followed for a fixed duration of 90 days after randomization). Assuming a 1-sided alpha of 0.025, not accounting for any dropouts from the study, and the interim analyses specified below, 1004 confirmed MACE (CV death, MI, or stroke) will provide at least 90% power. A 1-sided hypothesis test is necessary to differentiate directionality for interim analyses of futility and efficacy. Based on an assumed 90-day placebo event rate of 6.4%, an estimated 17,400 subjects (8700 per group) will be required.

The target number of events is also sufficient to achieve a 1-sided *P* value of 0.005 (approximate) with an observed hazard ratio of 0.85 in the primary endpoint and will afford at least 69% power to detect the minimally clinically relevant hazard ratio of 0.85.

The sample size calculation given above for number of required events and number of estimated subjects includes 3 formal interim analyses. The first 2 interim analyses will be conducted for futility only after observation of approximately 301 confirmed MACE (30% of the total target number of events) and 502 confirmed MACE (50% of the total target number of events). The third interim analysis will be conducted for efficacy only after observation of approximately 703 confirmed MACE (70% of the total target number of events).

The definition of futility boundary value is based on a 2-sided 95% confidence interval for the interim hazard ratio and a conclusion of no true underlying treatment difference will be reached if the confidence interval excludes a hazard ratio of 0.8 which is the hypothesized treatment effect. Specifically, the stopping boundary (non-binding) for futility will be crossed at the first interim analysis if the observed hazard ratio is ≥ 1.003 (1-sided *P* value ≥ 0.51), assuming the analysis is performed with 301 events. At the second interim analysis for futility, the stopping boundary on the hazard ratio scale is defined to be 0.953 (1-sided *P* value ≥ 0.295) assuming the number of events is exactly 50% of the target (502 events). The cumulative probabilities of meeting the futility thresholds at the first or second interim analyses if there is no true underlying treatment difference (ie, a true hazard ratio of 1) are 0.49 and 0.735, respectively.

Alpha-spending function from the Rho family [Kim and DeMets, 1987] with a parameter value of 16 will be utilized for the assessment of efficacy. At 70% of the planned event target (703 events), the stopping boundary for efficacy requires an approximate point estimate for the hazard ratio of < 0.753 or a 1-sided *P* value < 0.000083 assuming the interim analysis is conducted with exactly 703 events. Such a finding would provide robust and compelling evidence of treatment effect attributable to CSL112. The stopping boundary will be recomputed at the time of analysis using the actual number of events included in the interim analysis, and the specified spending function. Based on event accrual, if the expected timing of the IDMC review of the 70% interim analysis is less than 2 months prior to the anticipated completion of study enrollment, the 70% interim analysis for efficacy will not be conducted.

The sample size calculation was performed using East 6.4.

10.1.2 Re-estimation

MACE rates will be monitored using blinded data to reach a decision on the final sample size prior to completion of the enrollment phase. The observed blinded event rate will be based on a 90-day Kaplan-Meier (KM) estimate using a time-to-event approach with appropriate censoring to account for unobserved data. If the observed blinded event rate is higher than expected, then fewer subjects than 17,400 may be enrolled, with a minimum of approximately 15,000 subjects, corresponding to a placebo 90-day event rate of 7.4%. Conversely, if the observed, blinded event rate is less than expected, more subjects may be enrolled, but the increase would be capped at approximately 20,600 subjects, corresponding to a placebo 90-day event rate of 5.4%. The decision regarding sample size adjustment will be made when approximately 75% of subjects have been enrolled or approximately 75% of events have been accrued, whichever occurs first, with communication to sites occurring approximately 3 months prior to close of enrollment. The actual number of subjects to be enrolled, within the pre-specified sample size range (15,000 to 20,600), will be determined by the Executive Committee and CSLB and chosen to provide a total of approximately 1004 events for the primary outcome. At final reporting of study data, subgroup analysis to assess the consistency of primary MACE results for cohorts enrolled before and after the initial communication on sample size re-estimation will be performed.

10.2 Description of Study Analysis Sets

10.2.1 Screened Analysis Set

The Screened Analysis Set comprises all subjects who provide written informed consent.

10.2.2 Intent-to-Treat Analysis Set

The Intent-to-treat (ITT) Analysis Set comprises all subjects in the Screened Analysis Set who were randomized. The ITT Analysis Set will be analyzed using the treatment to which the subject was randomized, regardless of the treatment actually received.

Any subject who receives a treatment randomization number will be considered to have been randomized.

10.2.3 Modified Intent-to-Treat Analysis Set

The modified Intent-to-treat (mITT) Analysis Set comprises all subjects in the ITT Analysis Set who receive any amount of investigational product. The mITT Analysis Set will be

analyzed using the treatment to which the subject was randomized, regardless of the treatment actually received.

10.2.4 Safety Analysis Set

The Safety Analysis Set comprises all subjects in the ITT Analysis Set who receive any amount of the investigational product, and will be based on the actual treatment received. The safety set will be the primary analysis population for safety data.

10.3 Statistical Analyses and Methods

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan (SAP), which will be finalized before the database is locked.

10.3.1 Subject Disposition and Characteristics

10.3.1.1 Subject Disposition

The total number of subjects who were screened, randomized, completed the study, discontinued investigational product (including the reason), and withdrew consent from the study (including the reason) will be summarized. Screen failure rates will be presented by reason. The number of infusions received by each subject will be summarized. The data will be presented in summary tables by treatment group. The reason for discontinuing investigational product or withdrawing of consent from the study will be listed by subject. The duration of follow-up will be descriptively summarized across all subjects.

10.3.1.2 Subject Characteristics

All demographic and baseline characteristics summaries will be based on the ITT Analysis Set. They will be presented in summary tables by treatment group. Continuous data will be summarized by descriptive statistics, and categorical data will be summarized by frequency distributions. By-subject listings will be provided for demographic and baseline characteristic data.

10.3.2 Efficacy Analyses

The ITT Analysis Set will be the primary population for analysis of efficacy data.

10.3.2.1 Study Hypotheses

The study is designed with the objective of testing the null and the alternative hypotheses for the hazard ratio as defined below:

H_0: Hazard ratio (λ_T / λ_C) ≥ 1.0

H_1: Hazard ratio (λ_T / λ_C) < 1.0

Where: λ_T = hazard rate of MACE on the CSL112 group and λ_C = hazard rate of MACE on the placebo group. Under the null hypothesis, the assumption is that no beneficial effect is afforded by CSL112 while the alternative hypothesis states that CSL112 is effective in reducing the hazard rate of MACE relative to the placebo group.

10.3.2.2 Primary Efficacy Endpoint

The primary endpoint is defined as:

- Time to first occurrence of any component of the composite MACE, ie, CV death, MI, or stroke, from the time of randomization through 90 days.

All positively adjudicated MIs from randomization through 90 days will be included in the analysis of the primary endpoint. For each subject, time to event is defined as the time from randomization to the first occurrence of CV death, MI, or stroke based on CEC adjudicated and confirmed events. For subjects who do not have an event and do not complete the 90-day Follow-up Period, the censoring time is defined as the time from randomization to the last assessment at which it is confirmed that no event has occurred. For subjects who do not have an event or censoring time within the first 90 days after randomization, an administrative censoring will be applied at 90 days.

10.3.2.2.1 Primary Efficacy Analysis

The primary analysis of time to the 3-component MACE (CV death, MI, or stroke) will be based on a covariate-adjusted Cox regression model including fixed effects for treatment, region, index MI type, index MI management, age (as a continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and index MI management will be fitted using the PHREG procedure in SAS. The 1-sided Wald *P* value for hypothesis testing, the hazard ratio and its 2-sided 95% confidence interval, will be estimated from the model. The primary statistical analysis will utilize the ITT Analysis Set. Statistical significance will be assessed using a 1-sided 0.000083 alpha level at the efficacy interim look and 0.024999 at the final analysis (if the primary null

hypothesis is not rejected at the 70% interim analysis) assuming the number of events accrued is exactly the same as the target, ie, 703 and 1004 at the interim and final analyses, respectively. The actual significance level will be recomputed using an alpha spending function at the time of analysis if the observed number of events is different from that expected. Cumulative event rates will be calculated using the KM method. The effect over time will be illustrated with a plot of the complement (1 – KM) of KM estimates. Event counts and percentages will be summarized. Analysis under the ITT Analysis Set will utilize the strata to which subjects were randomized regardless of any errors in the randomization process.

10.3.2.2.2 Sensitivity Analyses of the Primary Endpoint

Additional sensitivity analyses of the primary endpoint will be performed to examine the robustness of the conclusion from the planned primary analysis to deviations from assumptions. Consistency of findings from the primary and sensitivity analyses will be investigated and clinical plausibility of findings examined. Sensitivity analyses will address the following categories of data:

- Informative censoring – Sensitivity to censored-at-random assumption will be examined to determine the impact of missing outcome data on the study conclusion in those subjects discontinuing the study prior to completing the 90-day duration of follow-up. The tipping point analysis for time to event endpoints as outlined in Lipkovich et al, 2016 will be used to investigate the departures from the censored-at-random assumption utilized in the primary analysis. For non-administratively censored observations, missing event times in the placebo arm will be imputed from completers in the same arm using a censored at random assumption whereas missing event times in the CSL112 arm will be imputed under increasingly higher hazards of MACE until the conclusion from the primary analysis is nullified. The clinical plausibility of the MACE hazard necessary to overturn the conclusion from the primary analysis will be examined.
- Reduced statistical model – this sensitivity analysis will be conducted without the prognostic variables which are included in the primary model (ie, age ≥ 65 years, diabetes, peripheral artery disease, or history of prior MI [excluding index MI]).The statistical analysis will be based on a covariate-adjusted Cox proportional hazards regression model including fixed effects for treatment, region, index MI type, index MI management, and a term for interaction between index MI type and index MI management. Thus, this model adjusts only for stratification factors and not for prognostic factors.

- Unadjusted statistical model – in this sensitivity analysis, the primary efficacy endpoint will be analyzed based on a Cox regression model including a covariate for treatment only.
- Receipt of investigational product – Sensitivity of results to whether the subject received any amount of the investigational product will be examined by repeating the primary analysis in the mITT Analysis Set.

10.3.2.3 Secondary Efficacy Endpoints

10.3.2.3.1 Key Secondary Efficacy Endpoints

The following key secondary efficacy endpoints are defined in the study and will be based on adjudication by the CEC:

- Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days.
- Time to first occurrence of CV death, MI, or stroke from the time of randomization through 180 days.
- Time to first occurrence of CV death, MI, or stroke from the time of randomization through 365 days.

10.3.2.3.1.1 Key Secondary Efficacy Analyses

Statistical analysis of key secondary endpoints will be based on the ITT Analysis Set utilizing an overall, 1-sided 0.025 significance level. The hypotheses associated with the key secondary endpoints will be formally tested and therefore adjusted for multiplicity as described in Section 10.3.2.5.

Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days:

A negative binomial regression model will be fitted to the count data arising from the number of hospitalizations. The model will include fixed effects for treatment, region, index MI type, index MI management, age (as a continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and index MI management. The log link function will be used and the log-transformed duration of follow-up within 90 days will be included in the model in order to account for the variable duration of follow-up across subjects. The mean rate of hospitalization per 90 days will be presented by treatment group. A 1-sided *P* value for treatment comparison, the rate

ratio (CSL112: Placebo) and its 2-sided 95% confidence interval will be estimated from the model. A cumulative plot of recurrent hospitalization events will be generated.

A sensitivity analysis of the hospitalization data will be performed to explicitly incorporate death into the outcome using the Win Ratio [Pocock et al, 2012] method. This approach recognizes clinical hierarchies within composite outcomes. With the planned endpoint, death will be weighted more heavily relative to the total number of CV hospitalizations during 90 days from the time of randomization. The unmatched win ratio (CSL112: Placebo) will be calculated along with associated 2-sided 95% CI and a 1-sided *P* value. A complete description of the analytical approach will be provided in the SAP.

In addition, hospitalizations per thousand subject-years will be summarized by treatment group for descriptive purposes.

Time to first occurrence of CV death, MI, or stroke from the time of randomization through 180 and 365 days:

Treatment comparison will be based on a covariate-adjusted Cox regression model which will be used to estimate the 1-sided Wald *P* value, the hazard ratio and its 95% confidence interval. The model will included fixed effects for treatment, region, index MI type, index MI management, age (as a continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and index MI management. The effect over time will be illustrated with a plot of the complement (1 - KM) of KM estimates. Event counts and percentages through 180 days will be presented by treatment group.

10.3.2.3.2 Other Secondary Efficacy Endpoints

The set of other secondary efficacy endpoints comprises:

- Time to first occurrence of each individual component of the composite primary efficacy endpoint from the time of randomization through 90 days (CV death, MI, Stroke).
- Time to first occurrence of CV death, type 1 MI, or stroke from the time of randomization through 90, 180, and 365 days.
- Time to occurrence of all-cause death from the time of randomization through 365 days.

The intent of analyzing the components of the composite primary endpoint is to provide information regarding the contribution of each component. The endpoints described in this section are not included in the formal hypothesis-testing framework described in Section 10.3.2.5 and therefore are not adjusted for multiplicity.

10.3.2.3.2.1 Other Secondary Efficacy Analyses

The other secondary efficacy endpoints will be analyzed similarly to the primary efficacy endpoint (ie, as time to event variables). With respect to the components of the primary composite, time to occurrence of each individual component will be analyzed and reported separately. Treatment comparison will be based on a covariate-adjusted Cox regression model for estimating the 1-sided Wald *P* value, the hazard ratio and its 95% confidence interval. The *P* values are intended to be descriptive. Event rates and percentages will be presented. The effect over time will be illustrated with the complement (1 – KM) of KM estimates.

10.3.2.4 Exploratory Efficacy Endpoints

The exploratory endpoints are defined as:

1. Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 30 days.
2. Time to first occurrence of CV death, MI, stroke, or severe coronary ischemia requiring urgent revascularization from the time of randomization through 90 days.
3. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 30 and 60 days.
4. Time to first occurrence of MI by type, according to the universal definition, from the time of randomization through 90 days.
5. Time to occurrence of CV death from the time of randomization through 365 days.
6. Time to occurrence of non-CV death from the time of randomization through 365 days.
7. Total occurrence of re-hospitalization for CV events and all-cause death from the time of randomization through 90 days.
8. Total occurrence of CV death, MI, and stroke from the time of randomization through 90, 180, and 365 days.
9. Total occurrence of all-cause death, MI, and stroke from the time of randomization through 90, 180, and 365 days.
10. Medical resource utilization from the time of randomization through 90 days:
    a. Number of total hospitalizations.
    b. Length of hospital stay.
    c. Number of CCU or ICU days.

d. Select procedures / surgeries related to hospitalization related to coronary, cerebral, or peripheral ischemia.

e. Discharge to home with additional care, home without additional care, rehabilitation, and skilled nursing facilities following hospitalization for coronary, cerebral, or peripheral ischemia.

11. Change in EQ-5D-3L data from baseline to Day 90.

10.3.2.4.1 Exploratory Efficacy Analyses

The analyses of the exploratory efficacy endpoints will be based on the ITT Analysis Set.

The total number of hospitalizations from the time of randomization through 30 days will be analyzed using a negative binomial regression model in a similar manner as described in Section 10.3.2.3.1.1 for the number of hospitalizations through 90 days.

The exploratory time to event efficacy endpoints listed in 2 to 6 above, will be analyzed in a manner similar to that of the primary endpoint (see Section 10.3.2.2.1). Treatment comparison will be based on a covariate-adjusted Cox regression model for estimating the 1-sided Wald *P* value, the hazard ratio and its 2-sided 95% confidence interval. The effect over time will be illustrated with a plot of the complement (1 – KM) KM estimates. Event counts and percentages will be presented.

The analysis of the endpoint, total occurrence of rehospitalizations for CV events and all-cause death from the time of randomization through 90 days, will be based on the unmatched Win Ratio [Pocock et al, 2012], as described in Section 10.3.2.3.1.

The exploratory endpoints including total occurrence of CV death, MI, and stroke from the time of randomization through 90, 180, and 365 days and total occurrence of all-cause death, MI, and stroke from the time of randomization through 90, 180, and 365 days will be analyzed using a negative binomial regression model in a similar manner as described in Section 10.3.2.3.1.1 for the number of hospitalizations through 90 days.

The relationship between medical resource utilization and treatment with CSL112 will be explored and characterized using descriptive statistics. For the purpose of data analysis, the medical resource utilization endpoints including number of hospitalizations, length of stay and days in ICU or CCU will be treated as count data. For each subject, the following results will be derived across all hospitalizations occurring during the 90 days from randomization: total number of hospitalizations, total number of days hospitalized and the total number of

days spent in ICU or CCU. The analysis of these endpoints will be performed using a negative binomial regression model in a similar approach to that described for CV hospitalizations. Treatment comparisons will be based on the resulting incidence ratio, 95% confidence interval, and 1-sided *P* value obtained from the model.

Following hospitalizations related to coronary, cerebral, or peripheral ischemia, counts of occurrences of discharge by category (to home with additional care, home without additional care, rehab, and skilled nursing facilities) will be summarized.

The EQ-5D-3L is a patient self-assessment of 5 dimensions of health-related quality of life: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each dimension is measured on a 3-point scale where a higher score corresponds to a worse health state. Scores from the individual dimensions will be utilized to calculate an overall utility score for each patient using the algorithm specified by the developers of the instrument [EuroQol Group, 1990]. The EQ VAS is a continuous 100-point integer scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

Response to each of the 5 dimensions will be descriptively summarized. For each treatment, shift tables will be employed indicating the number of subjects whose response falls into a grid defined by the baseline value on 1 axis and the post-treatment value on the other axis. To compare treatments on each dimension, the number (%) of subjects with improvement, no change, or worsening from baseline to the post-treatment value will be analyzed using a chi-square test for a 2 x 3 contingency table with ordered categories of response.

Both the utility score and the EQ VAS are continuous response variables describing the patient's self-assessment of their health status at baseline and post-treatment. Descriptive statistics including the mean, median, SD, minimum and maximum will be provided at baseline, post-treatment and for the change from baseline. The change from baseline will be compared between treatments employing an analysis of variance model including terms for treatment, index MI type, index MI management, region, an interaction term for index MI type by index MI management, age (as a continuous variable), diabetes, peripheral artery disease, and history of prior MI (excluding index MI).

10.3.2.5 Multiplicity

Issues related to multiplicity arising from testing the primary endpoint and key secondary endpoints will be addressed using the serial gatekeeping procedure [Dmitrienko et al, 2013] to control the overall experiment-wise error rate at a 1-sided 0.025 level. Three families of null hypotheses will be defined with family 1 consisting of the primary endpoint (ie, H_{01}),

family 2 consisting of the 2 key secondary endpoints (H_{02} and H_{03}), and family 3 consisting of the third key secondary endpoint (H_{04}). The null hypothesis associated with each of these endpoints is given below:

- H_{01}: Hazard ratio (CSL112:Placebo) for time to first CV death, MI, or stroke from the time of randomization through 90 days ≥ 1.0.
- H_{02}: The risk ratio (CSL112:Placebo) of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days ≥ 1.0.
- H_{03}: Hazard ratio (CSL112:Placebo) for time to first occurrence of CV death, MI, or stroke from the time of randomization through 180 days ≥ 1.0.
- H_{04}: Hazard ratio (CSL112:Placebo) for time to first occurrence of CV death, MI, or stroke from the time of randomization through 365 days ≥ 1.0.

If H_{01} is rejected at the interim analysis (ie, 1-sided $P < 0.000083$), then the hypothesis tests associated with the second family will be performed using the Hochberg procedure at 1-sided, 0.025 type I error level. The testing will proceed from the largest to smallest raw *P* value. Of the 2 *P* values, the larger will be compared with a 0.025 significance level; if significant ($P < 0.025$) then the remaining null hypothesis will also be rejected; otherwise, the smaller *P* value will be compared with a 1-sided significance level of 0.0125. Testing will proceed to family 3 (H_{04}) at a 1-sided 0.025 level only if both family 2 null hypotheses, H_{02} and H_{03}, are rejected.

If the formal testing process stops with family 1 or family 2 because of failure to achieve statistical significance, the remaining secondary outcomes will be considered as exploratory outcomes.

If the observed, 1-sided *P* value exceeds or is equal to the significance level at the efficacy interim analysis then the study will continue until 100% of events have been accrued. In this situation, testing of key secondary endpoints will be undertaken only at the final analysis using a 1-sided type I error of 0.025.

10.3.2.6 Subgroup Analysis

Internal consistency of observed treatment effect across major subgroups will be investigated as part of exploratory analyses. Subgroups may include, but are not limited to, groupings based on age, sex, region, ACS type (STEMI vs NSTEMI), whether managed with PCI or medically managed, subjects meeting modified enrichment criteria or not (diabetes mellitus on pharmacotherapy or at least 2 risk factors [age ≥ 65 years, prior history of MI, or

peripheral arterial disease]), prior PCI, renal function, and enrollment cohort relative to the communication date of sample size re-estimation to investigators (before or after). Further details will be provided in the SAP.

10.3.3 Safety Analyses

10.3.3.1 Extent of Exposure

The following data will be summarized by treatment group to describe the extent of exposure to investigational product.

An overall summary of the number of infusions administered and completed will be provided. Furthermore, each individual infusion will be described by providing the number of subjects starting an infusion, place and total volume (mL) of infusion administration, number of infusion interruptions, and total duration across all interruptions.

10.3.3.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities and summarized by system organ class and preferred term. Separate tables for AEs and SAEs, by severity (defined as mild, moderate, or severe) will be provided. In addition, AEs leading to discontinuation of investigational product, AEs leading to withdrawal of consent, or AEs leading to dose interruptions will be summarized.

A summary of AEs meeting any of the pre-specified criteria as described below will be generated:

- AEs that begin within 24 hours of the start of an infusion regardless of investigator causality assessment,
- All AEs that begin later than 24 hours of the start of an infusion and are considered to be at least possibly causally related to investigational product by the investigator or the Sponsor,
- AEs for which the investigator causality assessment is missing or indeterminate.
- AEs, for which the exposure-adjusted incidence rate in the CSL112 arm exceeds the exposure-adjusted incidence rate in the placebo arm by 30% or more on a relative basis, provided the difference in incidence rates is 1% or more.

10.3.3.3 Adverse events of special interest:

The following types of AEs are of special interest:

- Hypersensitivity: Standardized MedDRA Queries (SMQ) for hypersensitivity will be used to identify relevant preferred terms. The number (%) of subjects with SAEs and non-SAEs will be summarized.
- Acute kidney injury:
  - This AESI is defined based on laboratory values. Any increase in serum creatinine value of ≥ 0.3 mg/dL (27 μmol/L) from the baseline serum creatinine during the Active Treatment Period will be considered an event.
  - Any increase in serum creatinine value of ≥ 0.3mg/dL (27 μmol/L) from the baseline serum creatinine on 2 consecutive occasions during the Active Treatment Period will also be summarized.
  - Relevant preferred terms will be identified using the SMQ Acute Renal Failure, narrow and will be summarized as an additional analysis of kidney safety / injury.
- Potential hepatic injury:
  - This AESI is defined based on laboratory values. Any occurrence of either concomitant elevations of ALT > 3 x ULN with total bilirubin > 2 x ULN, or ALT > 5 x ULN will be considered an event. The number (%) of subjects with an event will be summarized.
  - In addition, potential drug-induced liver injury will be adjudicated by the CEC. The number (%) of subjects with a positively adjudicated event will be summarized.
- New or worsening HF – will be adjudicated by the CEC. The number (%) of subjects with positively adjudicated events will be reported.

10.3.3.4 Other Safety

Post-treatment changes in serum creatinine relative to baseline will be assessed to support the AKI AESI. Change from baseline will be categorized as ≤ baseline value, > 0 to < 0.3, ≥ 0.3 to < 0.5, and ≥ 0.5 mg/dL (44 μmol/L). The number (%) of subjects who achieve the threshold of rise in serum creatinine corresponding to ≥ 0.3 mg/dL (27 μmol/L) on 1 or more occasions as well as on 2 or more consecutive occasions will be presented. Increase relative to baseline will be categorized as ≥ 1.5 x baseline value, ≥ 2.0 x baseline value, ≥ 3.0 x baseline value. The number (%) of subjects with raw serum creatinine value ≥ 4.0 mg/dL (353.6 μmol/L) will be presented. The number (%) of subjects in each category and for each outcome will be presented by treatment arm.

Renal function will be further analyzed in subgroups defined on the basis of renal function categories and by time delay between contrast administration and investigational product administration, both alone and in combination. The 3 renal function subgroups are defined as normal (eGFR ≥ 90 mL/min/1.73 m^2), or mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m^2), and moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1.73 m^2). The 3 subgroups for time delay between administration of contrast and investigational product are defined as < 24 hours, 24 to < 48 hours, and ≥ 48 hours.

Of the subjects with blood samples assayed for anti-drug antibodies (ADA), the number (%) of subjects who are positive for binding antibodies to CSL112 and apoA-I will be summarized. Immunogenicity results for routine samples will be separately summarized from those samples taken to assess hypersensitivity reactions.

All other clinical laboratory assessments and vital sign measurements will be summarized using descriptive statistics. Actual value and change from baseline will be summarized by treatment arm. Further details will be provided in the SAP.

10.3.4 Pharmacokinetic Analyses

The following PK endpoints are planned as part of the exploratory objective:

- Baseline-corrected plasma apoA-I concentrations.
- Baseline-corrected plasma PC concentrations.
- Concentration in plasma at end-of infusion for apoA-I and PC.
- Accumulation ratio for apoA-I and PC.

Plasma concentrations of apoA-I and PC will be assayed from the blood samples drawn in the planned PK substudy. Accordingly, blood samples will be drawn before infusion 1, end of infusion 1, and end of infusion 4.Plasma concentrations will be descriptively summarized by treatment and nominal sampling time points. In addition, a population PK analysis will be conducted to further characterize the relationship between the plasma concentrations of apoA-I and PC and demographic and baseline characteristics, that will be reported separately.

10.3.5 Pharmacodynamic Analyses

The following pharmacodynamic endpoints are included to support the exploratory objective:

- Total cholesterol efflux.
- ABCA1-dependent efflux.
- ABCA1-independent efflux.

Blood samples for pharmacodynamic assessments will be drawn at the same as time points as PK blood draws. For each of these the above 3 endpoints, the change from baseline will be derived for each parameter and a 2 sample t-test will be used to compare the 2 treatment arms.

10.3.6 Interim Analysis

An IDMC will be convened to review accumulating efficacy and safety data. The statistical analysis and generation of relevant output will be performed by an external statistical data analysis center using the master randomization schedule provided by the IRT service provider. To preserve the integrity of the study blind, the results of the interim analyses will only be known to the IDMC. Any recommendation by the IDMC to terminate the study would not be based solely on statistical grounds. For either futility or efficacy interim assessments, a number of factors must be considered as part of the decision including exploring internal consistency across key subgroups, consistency across primary and key secondary endpoints, possible differences in prognostic factors between treatment groups and taking external information into account [Ellenberg et al, 2002]. The process for communicating the recommendations to the sponsor and the Executive Committee will be outlined in the charter. The key results of interim analyses will be summarized in the final clinical study report.

10.3.6.1 Interim Analysis of Futility and Efficacy Data

The IDMC will review efficacy data at 3 planned interim analyses and may recommend early termination of the study under the following conditions:

- There is strong evidence that CSL112 will fail to show superiority with respect to the primary MACE endpoint if the study is allowed to run to its planned completion (futility), given that the 2-sided 95% CI for the interim hazard ratio excludes 0.8, the hypothesized treatment benefit.
- There is strong evidence that CSL112 is superior to placebo with respect to the primary MACE endpoint (efficacy), based on crossing a threshold defined by the Rho alpha spending function with parameter of 16.

Of the 3 planned interim analyses, the first 2 interim analyses will be conducted after observation of approximately 301 confirmed MACE (30% of the total target number of events) and 502 confirmed MACE (50% of the total target number of events) and will be for futility only. The third interim analysis will be conducted after observation of approximately 703 confirmed MACE (70% of the total target) and will be for efficacy only. Events to be

counted toward the interim analysis targets will be adjudicated events from patients with at least 90 days of follow-up to ensure there is adequate representation across the full 90-day time period in the primary endpoint. Based on event accrual, if the expected timing of the IDMC review of the 70% interim analysis is less than 2 months prior to the anticipated completion of study enrollment, the 70% interim analysis for efficacy will not be conducted. If the 70% interim analysis is not conducted, an alpha adjustment will be applied as if it were conducted (ie, the alpha level for the final analysis will be 0.024999).

The decision rule for evaluating whether to stop the study due to futility (ie, no true underlying difference between treatments) will be based on the 2-sided 95% confidence limits for the observed hazard ratio at the interim look; futility will be concluded if the lower limit of the CI exceeds a hazard ratio of 0.8, the hypothesized treatment benefit. Assuming the futility looks are taken with exactly 301 (30% of the total target number of events) and 502 (50% of the total target) events, this futility rule corresponds to boundary values of ≥ 1.003 and ≥ 0.953 on the hazard ratio scale, respectively. These parameter values result in cumulative boundary-crossing probabilities of 0.49 and 0.735 for early stopping due to futility at the first or the second interim analysis, respectively, if there is no true underlying treatment difference. Equivalently, the futility boundary values on the 1-sided *P*-value scale correspond to ≥ 0.51 and ≥ 0.295 at the first and second interim looks for futility, respectively. The futility boundary does not represent a binding decision to stop the study should this boundary be crossed at either interim look.

For the purpose of evaluating whether to stop the study for efficacy, the Rho spending function with a parameter value of 16 represents a robust and compelling treatment difference as the observed hazard ratio at the efficacy interim look has to be approximately < 0.753, depending on the number of events included in the analysis.

For all interim analyses including futility (30% and 50%) and efficacy (70%), the assessment regarding whether the boundary is met will be based on an analysis using only subjects enrolled at least 90 days prior to the data cutoff date. The IDMC will also consider analyses including all subjects and events through 90 days, regardless of enrollment time. In addition to the analyses using adjudicated events, analyses based on investigator-events and 'best available' data will be reviewed. Best available MACE data includes the combination of MACE events that have been adjudicated and investigator-reported events that have not yet been through the adjudication process.

The stopping boundary values on the hazard ratio and *P* value scales given in Table 4 correspond to the number of confirmed events targeted at the interim and final analyses. The

efficacy boundary value may be recalculated using the rho alpha spending function at the time of analysis if the number of events accrued is different from that expected. The futility evaluation will be based on the confidence interval for the observed hazard ratio computed at the time of interim analysis.

Table 4 Stopping Boundary Values

Analysis	IF	Events	Cumulative α Spent	Boundary Values			
				Hazard Ratio Scale		1-Sided *P*-Value Scale	
				Efficacy	Futility	Efficacy	Futility
1	0.3	301	0	NA	≥ 1.003	NA	≥ 0.51
2	0.5	502	0	NA	≥ 0.953	NA	≥ 0.295
3	0.7	703	0.000083	< 0.753	NA	< 0.000083	NA
4	1.0	1004	0.025	< 0.884	≥ 0.884	< 0.024999	≥ 0.024999

IF = information fraction; NA = not applicable.

The boundaries are defined in East 6.4 to preserve 1-sided type I error at 2.5% under the assumption of a nonbinding futility rule.

In the event the efficacy stopping boundary is met at the third interim analysis, the IDMC will review key secondary endpoints, components (CV Death, spontaneous MI and stroke), and subgroups of the primary endpoint. Prior to recommending early termination of the study due to efficacy, the IDMC will ensure the presence of positive trends for key secondary endpoints and components of the primary MACE endpoint, as well as consistency across subgroups for the primary MACE endpoint. In addition to meeting the efficacy stopping boundary for the primary MACE endpoint, there will be a criterion for benefit in CV death or all-cause mortality, with details to be specified in the IDMC charter. In considering both efficacy data and safety data, an extremely compelling benefit / risk must be observed in order to recommend early stopping for efficacy.

If the study is terminated early for efficacy, a final analysis will be performed to account for data that have accrued during the conduct of the interim analysis and to test the key secondary endpoints. The results from the interim analysis where the efficacy threshold was met, as well as the final analysis, will be presented in the final clinical study report.

10.3.6.2 Analysis of Safety Data

The IDMC will evaluate the potential impact of CSL112 on hepatic and renal function and examine immunogenicity data for safety signals.

Central laboratory data for ALT and serum creatinine will be evaluated to assess the non-inferiority of CSL112 relative to placebo when approximately 20% of subjects have completed Visit 6 (Day 29).

Hepatic evaluation will be based on unconfirmed elevations in ALT (> 3 x ULN) at any time up to Day 29. The treatment difference in the incidence rates along with 2-sided 95% confidence interval for the treatment difference will be estimated. If the upper limit of the confidence interval is lower than the pre-specified non-inferiority margin of 3%, the hepatic effect of CSL112 will be considered to be non-inferior to placebo. In addition to evaluation of the non-inferiority analysis, the IDMC will review AEs that may be related to hepatic dysfunction (ie, right upper quadrant pain, anorexia, generalized pruritus, jaundice, and encephalopathy). The IDMC, using their clinical judgment and the outcome of non-inferiority evaluation, may recommend that central laboratory samples prior to infusions 2 and 3 be discontinued in the remaining subjects.

Renal evaluation will be based on the percentage of subjects with a change from baseline (before infusion 1) in serum creatinine ≥ 0.3 mg/dL (27 μmol/L) at any time up to Day 29. The treatment difference in the incidence rates along with a 2-sided 95% confidence interval for the treatment difference will be estimated. If the upper limit of the confidence interval is lower than the pre-specified non-inferiority margin of 5%, the renal impact of CSL112 will be considered to be non-inferior to placebo. The IDMC has the discretion to recommend that laboratory samples in remaining subjects be discontinued.

In addition to the non-inferiority assessment detailed above, the IDMC will conduct subgroup analyses by renal function categories and by time delay between contrast and investigational product administration, both alone and in combination. The renal function subgroups will be based on the following 3 eGFR categories: normal renal function (eGFR ≥ 90 mL/min/1.73 m^2), mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m^2), and moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1.73 m^2). Within the moderate renal impairment subgroup, additional analyses will be performed by degree of CKD Stage 3 (ie, CKD 3a (eGFR ≥ 45 to < 60 mL/min/1.73 m^2) versus CKD 3b (eGFR ≥ 30 to < 45 mL/min/1.73 m^2). The 3 subgroups for time delay between contrast and investigational product administration will be: < 24 hours, 24 to < 48 hours, ≥ 48 hours). Within each of the 9 subgroups defined above, the IDMC will review the following summary statistics: event rates by treatment, the treatment difference in event rates, and the 95% CI for the treatment difference in event rates. The summary statistics for each of the component subgroups will be reviewed as well:
3 subgroups based on renal function and 3 subgroups based on time delay between contrast

administration and investigational product administration. Summaries of increases occurring on 1 or more occasions as well as on 2 or more consecutive occasions will be presented. For the subgroup with moderate renal impairment and a time delay between administration of contrast and investigational product that is < 24 hours, the IDMC will review data after each 20 subjects are enrolled in this subgroup and reach Day 29 in order to assess for any possible effect of the investigational product on renal function. The reviews of this individual subgroup will continue until the IDMC determine they are no longer necessary.

The non-inferiority assessment will serve as a minimum criterion for a potential IDMC decision to discontinue routine assessments of renal function prior to infusions 2 and 3. Prior to a decision to discontinue routine assessments of renal function at infusions 2 and 3, the IDMC will also utilize clinical judgment, considering the summary of results for the subgroups outlined above. The IDMC will also use clinical criteria and will review AEs that are related to AKI, defined as AEs with a MedDRA Preferred Term included in the Acute Renal Failure narrow SMQ. Before any decision, the IDMC will also apply medical judgment to assess severity, reversibility and a change to the benefit-risk balance. After this planned interim renal evaluation, the IDMC will have the option to recommend discontinuing or continuing renal assessments prior to infusions 2 and 3 in the overall study population or in certain subgroups of either renal function (such as moderate renal impairment), or time interval between contrast administration and administration of investigational product. For example, if data are insufficient in a certain subgroup, the recommendation can be appropriately tailored to ensure adequate safety monitoring in all subgroups of subjects.

Blood samples drawn from approximately the first 600 subjects (approximately 300 CSL112 and 300 placebo) or in the event of a serious hypersensitivity reaction will be assayed to detect the presence of binding antibodies to CSL112 and apoA-I. Samples from 300 subjects who receive CSL112 will provide a 95% probability of observing at least 1 positive result if the underlying rate is 1/100 (ie, 1%). If no immunogenicity signal is observed in CSL112-treated subjects, the IDMC chair may recommend that no further samples be assayed although samples will be collected from all enrolled subjects at baseline and Visit 6 and stored. The IDMC may also recommend continued assay of immunogenicity samples in an additional subset of subjects based on other safety concerns whether or not immunogenicity signal is observed. The number (%) of subjects with positive results for binding antibodies will be presented.

11 Quality Assurance

The study may be subject to an audit by CSLB, an authorized representative(s) of CSLB and / or inspections by an authorized regulatory authority (eg, US Food and Drug Administration [FDA]). Regulatory authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSLB will notify the investigator of any upcoming audit / inspection.

In the event of an audit, all pertinent study-related documentation must be made available to the auditor(s). If an audit or inspection occurs, the investigator at each study site will permit the auditor / inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

12 Regulatory and Ethics Considerations

12.1 Regulatory Considerations

CSLB or its agents will submit the appropriate documents to the local regulatory agencies before study start.

This study will be conducted under an appropriate regulatory submission and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this study protocol are designed to ensure that CSLB and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 R2 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

12.2 Institutional Review Board / Independent Ethics Committee

The investigator must submit the protocol and ICFs for review by an authorized and properly constituted (according to local guidelines) IRB / IEC. Written approval must be received from the IRB / IEC before commencement of the study.

12.3 Subject Information and Informed Consent

Informed consent of study subjects according to the standards of GCP must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form and should be deemed appropriate and approved by

the IRB / IEC. Subjects (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

The subject (or if necessary, legally acceptable representatives) must be provided with a copy of the signed ICF.

Should there be any amendments to the protocol that would directly affect the subject's participation in the study (eg, a change in any procedure), the ICF must be amended to incorporate this modification. Subjects must be informed of the change and they must sign the amended ICF indicating that they re-consent to participate in the study.

12.4 Subject Confidentiality

All subject names and contact details will be kept confidential. Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. Each subject will be told that all study findings will be handled in the strictest confidence.

The investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, phone number and identity in the study) so that regulatory agencies or CSLB may access this information should the need arise. These records should be retained in a confidential manner as long as legally mandated according to local requirements.

Subject medical records pertaining to the study may be inspected / audited at any time by CSLB employees or their duly authorized representatives, a regulatory authority or the IRB / IEC. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections / audits.

12.5 Indemnity and Compensation

CSLB has taken out insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding compensation and the obligations of the investigator / CSLB are provided in the Clinical Trial Research Agreement for the study (see Section 13.1).

13 Administrative Considerations

13.1 Clinical Trial Research Agreement

This study will be conducted under a Clinical Trial Agreement between CSLB ("Sponsor") and the institution(s) representing the investigational study site(s) ("Authority"). Financial support to the investigational site(s) will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and CSLB, and will form the contractual basis under which the clinical study will be conducted.

13.2 Clinical Study Registration and Results Disclosure

CSLB will provide the relevant study protocol information in public database(s) before or at commencement of the study. CSLB may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record.

13.3 Implementation of the Protocol / Protocol Amendment(s)

With the exception of medical emergencies, no changes or deviations in the conduct of the signed protocol will be permitted without documented approval of the CSLB Medical Monitor or designee and the IRB / IEC. In the event of a medical emergency, the investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the CSLB and the IRB / IEC.

Modifications to the protocol that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB / IEC.

Administrative changes to the protocol, defined as minor corrections and / or clarifications that have no effect on the way the study is to be conducted, will not require IRB / IEC approval, but will be submitted to the IRB / IEC for their information.

13.4 Protocol Deviations

All instances where the critical requirements of the study protocol were not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of

the investigator and / or CSLB. Study protocol deviations arise when either subjects who have been entered in the study and / or the study sites deviate from the IEC / IRB-approved study protocol.

A major protocol deviation is any significant divergence from the protocol that could have a significant effect on the subject's safety, rights, or welfare and / or on the integrity of the study data **(**ie, nonadherence on the part of the subject, the investigator, or the sponsor to protocol-specific inclusion / exclusion criteria, and / or GCP guidelines). If a major protocol deviation occurs, the investigator must notify CSLB designee and the appropriate IRB / IEC as soon as possible or as per local regulation. Major protocol deviations will be tracked.

13.5 Documentation and Record Keeping

13.5.1 Data Collection

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, or physical examinations, administration of investigational product or concomitant therapy, any AEs experienced, and other notes as appropriate. These records (electronic or paper) constitute source data.

Electronic CRF entries will be considered source data if the eCRF is the site of the original recordings (ie, there is no other written or electronic record of the data).

An eCRF will be provided by CSLB (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be backed up by source data unless the eCRF is considered source data. All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

13.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the eCRFs checked against the subject records for completeness and accuracy. The investigator must provide direct access to source data documents. CSLB's study monitor or delegate will perform this function.

Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Queries will be generated for

questionable data and clarification sought from the investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

13.5.3 Record Retention

The investigator must follow the principles for record retention outlined in the Clinical Trial Research Agreement. An investigator study file prepared by CSLB (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. All study documentation and materials maintained in the investigator study file must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the investigator study file at the study site must be available for inspection by CSLB's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from CSLB or a competent regulatory authority.

Following completion of the study, the investigator is responsible for archiving the investigator's study file, the subject's records and the source data according to applicable regulatory requirements.

13.6 Study and Site Closure

CSLB reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the CSLB Study Monitor (or delegate) will discuss this with the investigator at each study site at that time and notify the investigators in writing. If the study is suspended or terminated for safety reasons, all investigators and the relevant regulatory agencies will be immediately notified of the action as well as the reason for the suspension / termination. The investigator at each study site will advise their IRB / IEC overseeing the study of the suspension / termination.

13.7 Clinical Study Report

A clinical study report will be written after the completion of the study. CSLB or its agent will write the report in consultation with the investigator or, if applicable, a nominated coordinating investigator (or delegate). It is required by CSLB that the coordinating investigator will sign the clinical study report.

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

13.8 Use of Data and Publications

The rights and obligations of investigators and CSLB concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study.

14 References

Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64(24):e139-228.

Center for Drug Evaluation and Research, Approval Package for Application Number: NDA 22-433/S015. Brilinta® (ticagrelor). AstraZeneca Pharmaceuticals LP 9/03/2015.

Chenevard R, Hürlimann D, Spieker L, Béchir M, Enseleit F, Hermann M, et al. Reconstituted HDL in acute coronary syndromes. Cardiovascular therapeutics 2012;30e51-7.

CPMP/EWP/570/98. Guideline on clinical investigation of new medicinal products for the treatment of acute coronary syndrome (CPMP/EWP/570/98). 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/04/WC500205365.pdf.

Dmitrienko A, Ralph, B, D'Agostino, Huque MF. Key multiplicity issues in clinical drug development. Statist Med. 2013;32(7):1079-111.

Ellenberg SS, Fleming TR, DeMets DL. Data monitoring committees in clinical trials: a practical perspective. John Wiley & Sons, Ltd. Chichester, UK:2002.

Epstein JS, Zoon KC. Important drug warning: immune globulin intravenous (human) (IGIV) products. Neonatal Netw. 2000;19(2):60-2.

Finfer, S. Clinical controversies in the management of critically ill patients with severe sepsis: resuscitation fluids and glucose control. Virulence. 2014;5(1):200-5.

Gelmont D, Thomas RG, Britt J, Dyck-Jones JA, Doralt J, Fritsch S, et al. Demonstration of safety of intravenous immunoglobulin in geriatric patients in a long-term, placebo-controlled study of Alzheimer's disease. Alzheimer's and dementia: Translational research and clinical interventions. 2016;2(2):131-9.

Gibson CM, 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;134(24):1918-30.

Gille A, Easton R, D'Andrea D, Wright SD, Shear CL. CSL112 enhances biomarkers of reverse cholesterol transport after single and multiple infusions in healthy subjects. Arterioscler Thromb Vasc Biol. 2014;34(9):2106-14.

FDA. Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009.

Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med. 2011;364:127-35.

Kim K, DeMets DL. Design and analysis of group sequential tests based on the type I error spending rate function. Biometrika. 1987;74(1):149-54.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Lipkovich I, Ratitch B, and O'Kelly M. Sensitivity to censored-at-random assumption in the analysis of time-to-event endpoints. Pharmaceut. Statist. 2016,15:216-29.

Liu C, Zhang Y, Ding D, Li X, Yang Y, Li Q, et al. Cholesterol efflux capacity is an independent predictor of all-cause and cardiovascular mortality in patients with coronary artery disease: A prospective cohort study. Atherosclerosis. 2016;249:116-24.

Mahoney EM, Wang K, Cohen DJ, Hirsch AT, Alberts MJ, Eagle K, et al. One-year costs in patients with a history of or at risk for atherothrombosis in the United States. Circ Cardiovasc Qual Outcomes. 2008;1(1):38-45.

Morrow DA. Cardiovascular risk prediction in patients with stable and unstable coronary heart disease. Circulation. 2010;121(24):2681-91.

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics – 2016 update: a report from the American Heart Association. Circulation. 2016;133(4):447-54.

O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction:: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. CF/AHA Task Force. Circulation. 2013;127(4):529-55.

Pocock SJ,Ariti, CA Collier TJ, Wang D. The Win Ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European Heart Journal. 2012;33,176-82.

Relkin, NR, Thomas, RG, Rissman, RA, Brewer, JB, Rafii, MS, van Dyck, CH, et al. A phase 3 trial of IV immunoglobulin for Alzheimer disease. Neurology. 2017;88(18):1768-75.

Remaley AT, Amar M, Sviridov D. HDL-replacement therapy: mechanism of action, types of agents and potential clinical indications. Expert Rev Cardiovasc Ther. 2008;6(9):1203-15.

Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med. 2014;371(25):2383-93.

Saleheen D, Scott R, Javad S, Zhao W, Rodrigues A, Picataggi A, et al. Association of HDL cholesterol efflux capacity with incident coronary heart disease events: a prospective case-control study. Lancet Diabetes Endocrinol. 2015;3(7):507-13.

Siddiqi HK, Kiss D, Rader D. HDL-cholesterol and cardiovascular disease: rethinking our approach. Curr Opin Cardiol. 2015;30(5):536-42.

Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, et al. Comparative performance of the CKD epidemiology collaboration (CKD-EPI) and the modification of diet in renal disease (MDRD) study equations for estimating GFR levels above 60 mL/minute/1.73 m^2. Am J Kidney Dis. 2010;56(3):486-95.

Tall AR. An overview of reverse cholesterol transport. Eur Heart J. 1998;19(Suppl A):A31-5.

Tardif JC, Gregoire J, L'Allier PL, Ibrahim R, Lesperance J, Heinonen TM, et al. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA. 2007;297(15):1675-82.

Tardif JC, Heinonen T, Noble S. High-density lipoprotein/apolipoprotein A-I infusion therapy. Curr Atheroscler Rep. 2009;11(1):58-63.

The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy. 16(3):199-208.

Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Mickley H, Crea F, Van de Werf F, Bucciarelli-Ducci C. Fourth universal definition of myocardial infarction (2018). European heart journal. 2019 Jan 1;40(3):237-69.

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.

Yusuf S, Phil D, Mehta SR, Chrolavicius S, Afzal R, Pogue J, , et al. Fifth organization to assess strategies in acute ischemic syndromes investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354(14):1464-76.

Zhang J, Xu J, Wang J, Wu C, Xu Y, Wang Y, et al. Prognostic Usefulness of Serum Cholesterol Efflux Capacity in Patients With Coronary Artery Disease. Am J Cardiol. 2016;117:508-14.

15 Appendices

Appendix 1 Signatures

Signature on Behalf of Sponsor

Study Title:	A phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of CSL112 in subjects with acute coronary syndrome.
Protocol Number:	CSL112_3001

I have read the Clinical Study Protocol titled "A phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of CSL112 in subjects with acute coronary syndrome" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

(Signa[redacted])

PPD

Date (DD MMM YYYY)

PPD

(Printed name)

PPD

(Title)

Signature of Principal Investigator

Study Title:	A phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of CSL112 in subjects with acute coronary syndrome.	
Protocol Number:	CSL112_3001	Site Number:

I have read the Clinical Study Protocol titled "A phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of CSL112 in subjects with acute coronary syndrome".

By signing this Clinical Study Protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the Clinical Study Protocol, the standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and applicable regulatory requirements.

Changes to the Clinical Study Protocol will only be implemented after written approval is received from CSL Behring (CSLB) and the Institutional Review Board or Independent Ethics Committee (as appropriate) with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the Clinical Study Protocol.

_____ _____

(Signature) Date (DD MMM YYYY)

_____

(Printed name)

_____

(Title)

Appendix 2 Modified Rankin Score

The modified Rankin score should be assessed at the time of stroke occurrence for subjects with a suspected or confirmed stroke.

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

References:

Rankin J. Cerebral vascular accidents in patients over the age of 60. Scott Med J. 1957;2:200-15.

Bonita R. and Beaglehole R. Modification of Rankin Scale: Recovery of motor function after stroke. Stroke. Dec. 1988;19(12):1497-1500.

Van Swieten JC, Koudstaal PJ, Visser, MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19(5):604-7.

Signature Page

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Signed By	Date (GMT)
PPD	11-Sep-2019 15:06:38
Approved-PPD Approval	
PPD	11-Sep-2019 15:42:20
Approved-PPD Approval	
PPD	11-Sep-2019 16:00:13
Approved-PPD Approval	

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