CLINICAL STUDY PROTOCOL

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

Study Number:	CSL112_2001
Study Product:	CSL112 (Reconstituted High Density Lipoprotein)
Development Phase:	2
Sponsor:	CSL Behring LLC (CSLB) 1020 First Avenue King of Prussia PA 19406-0901
Protocol Version:	FINAL V2.0, Amendment 1
EudraCT Number:	2015-003017-26
IND Number:	CCI
Protocol Date:	6 June 2016
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki 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.

SIGNATURE ON BEHALF OF SPONSOR

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

Protocol Number: CSL112_2001

I have read Amendment 1 to the protocol CSL112_2001 titled "A Phase 2, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group, Study to Investigate the Safety and Tolerability of Multiple Dose Administration of CSL112 in Subjects with Moderate Renal Impairment and Acute Myocardial Infarction" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD
PPD

MD, FACC

Date
(DD MMM YYYY)

SIGNATURE OF INVESTIGATOR

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

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By signing this 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 protocol, the principles of the Declaration of Helsinki (2008), the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and applicable regulatory requirements.

Changes to the protocol will only be implemented after written approval is received from CSL Behring LLC (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 protocol.

_____ _____

Investigator Signature Date (DD MMM YYYY)

_____

Printed Investigator Name

_____

Affiliation of Investigator

Protocol Synopsis

Title	A Phase 2, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group, Study to Investigate the Safety and Tolerability of Multiple Dose Administration of CSL112 in Subjects with Moderate Renal Impairment and Acute Myocardial Infarction
Study Number	CSL112_2001
Sponsor	CSL Behring LLC (CSLB)
Development Phase	2
Study Product	CSL112 (Reconstituted High Density Lipoprotein)
Indication	Reduction of early recurrent atherothrombotic events in acute myocardial infarction patients (ST segment elevation myocardial infarction [STEMI] or non-ST segment elevation myocardial infarction [NSTEMI]) who are at high risk of subsequent events.
Study Summary	CSL112 drug product resembles nascent high density lipoprotein (HDL). It is a novel formulation of apolipoprotein A-I (apoA-I), phosphatidylcholine (PC), and cholate; and is stabilized by sucrose. CSL112 is being developed for the reduction of recurrent cardiovascular (CV) events after acute myocardial infarction (AMI). The premise of the CSL112 mechanism of action and the resulting treatment strategy is that infusion of apoA-I after the index ACS event, and during the subacute period after the event, will reduce the size and/or instability of atherosclerotic plaque, thereby reducing the risk of plaque rupture or erosion that would lead to a recurrent CV event in patients with AMI. Renal impairment (RI) is a prevalent and increasingly common concurrent condition in patients with AMI. Patients who experience an AMI event are at high risk for a recurrent CV event and mortality is inversely related to renal function status: subjects with mild, moderate, and severe RI have, respectively, progressively poorer long-term prognosis as compared with patients with normal renal function. As the number of AMI patients with RI is relatively high (~15% to 30%) (Gibson et al, 2004; Fox et al, 2010), the identification of therapies that are safe and effective in these patients would represent an important advancement in medical therapy. This study is a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the safety and tolerability of up to 4 weekly intravenous (IV) administrations of CSL112 compared with placebo in subjects with moderate RI (estimated glomerular fitration rate [eGFR] ≥ 30 and < 60 mL/min/1.73 m^2) and acute myocardial infarction (AMI).

	CSL112 drug product 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 intravenous (IGIV) products formulated with sucrose were administered at high doses or high rates of administration (Epstein and Zoon, 2000). Thus, evaluation of the renal safety of CSL112 is warranted, specifically in the subpopulation of patients with moderate RI who have experienced a recent AMI event. No renal safety concerns were identified in the 4 completed CSL112 phase 1 and-2a-studies, including a phase 1 multicenter center, double-blind, placebo-controlled, ascending single-dose phase 1 study in adult subjects with moderate RI (eGFR ≥ 30 and < 60 mL/min/1.73 m^2) and in healthy adult subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) (Study CSL112_1001). In addition, a phase 2b study (Study CSLCT-HDL-12-77), a multicenter, randomized, placebo-controlled study to investigate the hepatic and renal safety and tolerability of multiple dose administration of 2 IV infusion regimens of CSL112 versus placebo in approximately 1200 subjects with acute myocardial infarction (AMI) was initiated in the third quarter of 2014 and completed in the first quarter of 2016. To date, the program level Data and Safety Monitoring Board (DSMB) has reviewed safety and pharmacokinetic (PK) data from the Active Treatment Period after 5%, 10%, 25%, 50%, and 75% of subjects were enrolled, and recommended the study continue without change. Data are not yet available for this study. Further evaluation of the safety and tolerability of multiple dose administration of CSL112 in subjects with moderate RI and AMI are warranted before inclusion of this population in a phase 3 morbidity and mortality outcomes trial. This phase 2 study is intended to characterize the renal risk profile of CSL112 in subjects with moderate RI who have experienced a recent AMI. The occurrence of clinically important renal serious adverse events (SAEs) as reported by the Investigator and AKI will be evaluated. In subjects with moderate RI who have undergone percutaneous coronary intervention (PCI), the occurrence of AKI as defined by the Acute Kidney Injury Network (AKIN) criteria is approximately 10% (Tsai et al, 2014). After excluding subjects with evidence of AKI at screening, the occurrence of renal SAEs and AKI will be assessed in this post-AMI moderate RI patient population.
Primary Objective(s)	To assess the renal safety of CSL112 in subjects with moderate RI and AMI after administration of up to 4 weekly infusions of CSL112.
Primary Endpoint(s)	Co-primary endpoints of the incidences of treatment-emergent: 1. Renal SAEs, defined in Section 2.1.2 2. AKI, defined as an absolute increase in serum creatinine from baseline of ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period that is sustained upon repeat measurement by the central

	laboratory no earlier than 24 hours after the elevated value. If no repeat value is obtained, a single serum creatinine value that is increased from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period would also fulfil the definition of AKI. Treatment-emergent is defined as occurring at or after the start of the first infusion. Baseline for determination of AKI is defined as the pre-infusion central laboratory serum creatinine level on Study Day 1.
Secondary Objective(s)	Secondary objectives of the study are: 1. To further characterize the safety and tolerability of CSL112 in subjects with moderate RI and AMI. 2. To characterize the PK of CSL112 after multiple dose administration in subjects with moderate RI and AMI.
Secondary Endpoint(s)	Secondary safety and tolerability endpoints include: 1. The occurrence of any treatment-emergent adverse event (TEAE) throughout the study 2. Occurrence of treatment-emergent adverse drug reactions or suspected adverse drug reactions defined as: a. All TEAEs, including local tolerability events, that begin during or within 1 hour after the end of an infusion, or b. Those TEAEs which the Investigator or Sponsor indicates may be causally related to the administration of the investigational product (CSL112 or placebo), or c. All TEAEs for which the Investigator's causality assessment is missing or indeterminate, or d. All TEAEs for which the incidence in an active treatment arm exceeds the exposure-adjusted incidence rate in the placebo arm by 30% or more, provided the difference in incidence rates is 1% or more. 3. Changes from baseline (ie, pre-infusion on Study Day 1) through to the end of the Active Treatment Period in renal status defined as: a. Absolute increases from baseline in serum creatinine as follows: i. ≤ baseline value ii. > 0 to < 0.3 mg/dL iii. ≥0.3 to ≤0.5 mg/dL iv. > 0.5 mg/dL b. Increases in serum creatinine that are sustained for

≥ 24 hours upon repeat measurement as follows:

i. ≥ 1.5 x baseline value

ii. ≥ 2 x baseline value

iii. ≥ 3.0 x baseline value

iv. serum creatinine ≥ 4.0 mg/dL (353.6 µmol/L)

c. Initiation of renal replacement therapy

d. Decrease in eGFR ≥ 25% from baseline starting during the Active Treatment Period and that is sustained at the final study visit

4. Change from baseline (ie, after infusion on Study Day 1) in hepatic status that occurs during the Active Treatment Period and that are sustained for ≥ 24 hours upon repeat measurement as follows:

   a. Alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN)

   b. ALT > 5 x ULN

   c. ALT > 10 x ULN

   d. Serum total bilirubin > 1.5 x ULN (Note: For subjects with a history of Gilbert's syndrome, this assessment will be based on indirect bilirubin.)

   e. Serum total bilirubin > 2 x ULN (Note: For subjects with a history of Gilbert's syndrome, this assessment will be based on indirect bilirubin.)

   f. Possible Hy's Law cases, as defined in the FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009; see Section 9.1.3.3 for definition of Hy's Law)

5. The occurrence of treatment-emergent bleeding events as defined by the Bleeding Academic Research Consortium (BARC) criteria (Mehran et al, 2011) from start of the first infusion until the end of the Safety Follow-up Period.

6. Clinically significant changes in clinical laboratory test results (serum biochemistry, hematology, and urinalysis), physical examination findings, body weight, electrocardiograms (ECGs), and vital signs (blood pressure, pulse rate, and body temperature).

7. The occurrence of binding antibodies specific to apoA-I and/or CSL112.

Secondary PK endpoints include:

1. Baseline (ie, pre- infusion on Study Day 1)-corrected plasma apoA-I

	concentrations 2. Baseline-corrected plasma PC concentrations 3. Concentration in plasma at End-of-Infusion for apoA-I and PC 4. Accumulation ratio (R) for apoA-I and PC
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
Study Design	This is a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and tolerability of up to 4 weekly IV administrations of 6 g CSL112 compared with placebo in subjects with moderate RI and AMI. The main study will enroll approximately 81 subjects who will be randomly assigned in a 2:1 ratio to receive 6 g CSL112 (54 subjects) versus placebo (27 subjects). To ensure that at least one-third of the study population has an eGFR in the Chronic Kidney Disease (CKD) 3b range (30 to < 45 mL/min/1.73 m^2), no more than two-thirds of the study population will have an eGFR in the CKD 3a range (45 to < 60 mL/min/1.73 m^2). Randomization of the 81 subjects will be stratified by eGFR (30 to < 45 mL/min/1.73 m^2 or 45 to < 60 mL/min/1.73 m^2) as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and by medical history of diabetes requiring current treament with any anti-diabetic medication (yes or no). Clinical procedures for these subjects will include assessments for safety (including renal and hepatic), PK, and CCI [redacted]

CCI [redacted]

A summary of study assessments and procedures by visit is shown in the Schedule of Assessments. The study will consist of screening and 2 study periods: an Active Treatment Period (approximately 29 days) and a Safety Follow-up Period (approximately 30 days from the end of the Active Treatment Period). Subjects will be assessed for eligibility during screening and up to and including randomization (Visit 1 and Visit 2 before infusion), which must occur within 5 days after first medical contact (FMC) for the index AMI. Eligible subjects meeting all inclusion criteria and none of the exclusion criteria will receive four 2-hour IV infusions of investigational product (6 g CSL112 or placebo), a minimum of 7 days apart, during a 4-week Active Treatment Period.

Before the first infusion of investigational product, the subject must be clinically stable, have hepatic function tests within acceptable limits, and have documented evidence of stable renal function and no suspicion of AKI at least 12 hours after FMC for the index AMI; for those subjects undergoing angiography, with or without PCI, renal function must be documented to be stable at least 12 hours after administration of IV contrast agent (see eligibility criteria below).

Screening and randomization of subjects may occur on the same day (Study Day 1 of the Active Treatment Period) provided that the minimum time window after FMC for the index event or administration of IV contrast agent (for subjects undergoing angiography) is adhered to for assessment of stability of renal function before administration of the first infusion of investigational product (Section 8.2.1.2 and Section 8.2.2.1).

Ongoing eligibility for all subsequent infusions of investigational product will be confirmed before each infusion and will include assessments of renal and hepatic function (Section 8.2.2.2). Each infusion should be completed as close to the protocol-specified visit schedule as possible, ie, no fewer than 7 days and no more than 10 days between each infusion. An infusion may be skipped or delayed at the discretion of the Investigator if more time is necessary to confirm renal function stability or to evaluate and treat an AE before the next infusion (Section 8.2.2.2). If an infusion is skipped or delayed for a medical or safety reason, the medical monitor should be contacted for further guidance.

The end of the Active Treatment Period occurs upon completion of Visit 7 (Study Day 29). The Safety Follow-up Period (duration of approximately 30 days) will begin immediately after Visit 7. Subjects will return to the study clinic at Visit 8 (Study Day 60) for assessment of AEs and other safety procedures.

Number of Subjects	Approximately 81 subjects will be enrolled into this study.
Study Duration	The maximum duration of the study for an individual subject is expected to be approximately 9 weeks. This estimation is based on: • a 5-day Screening Period • a 4-week Active Treatment Period • a 4-week Safety Follow-up Period The overall study duration (ie, first subject's screening visit to last subject's end of study visit) is estimated to be approximately 9 months.
Study Population and Main Criteria for Eligibility	Men or women at least 18 years of age with moderate RI (eGFR $\geq$ 30 and $<$ 60 mL/min/1.73 m^2, as calculated by the CKD-EPI equation). Subjects must also have evidence of myocardial necrosis in a clinical setting consistent with a type I (spontaneous) AMI as defined by the following: • 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, • Any 1 or more of the following: – Symptoms of ischemia – New (or presumably new) significant ST/T wave changes or left bundle-branch block (LBBB) – Development of pathological Q waves on ECG – Imaging evidence of new loss of viable myocardium or regional wall motion abnormality – Identification of intracoronary thrombus by angiography Before the first infusion of investigational product, the subject must be clinically stable, have hepatic function tests within acceptable limits, and have documented evidence of stable renal function and no suspicion of AKI at least 12 hours after FMC for the index AMI. For subjects undergoing angiography, with or without PCI, stable renal function is defined as a serum creatinine value at least 12 hours after IV contrast administration that is increased $<$ 0.3 mg/dL from the pre-contrast administration value. If the local laboratory post-contrast serum creatinine value is increased $\geq$ 0.3 mg/dL from the pre-contrast administration value, the laboratory test may be repeated once at least 24 hours after the initial assessment to determine eligibility and stable renal function. The repeat serum creatinine value must be increased $<$ 0.3 mg/dL from the pre-contrast administration value and there must be no clinical suspicion of AKI for the subject to be eligible to receive the first infusion (Table 7).

Study Product Dose, Dosing Regimen and Administration	Based upon the results of the phase 1 PK and safety study in subjects with moderate RI (Study CSL112_1001), a dose of 6 g CSL112 has been selected for this study. CSL112 will be administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (4 infusions total).
Comparator Product, Dose, Dosing Regimen and Administration	Placebo control (0.9% weight/volume sodium chloride solution, ie, normal saline) administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (4 infusions total) in a volume matched to the CSL112 infusion volume (CCI).
Safety Assessments	Monitoring of all AEs, ECGs, physical examination findings, body weight, vital signs (blood pressure, pulse rate, body temperature), clinical laboratory tests (serum biochemistry, hematology [including hemolysis, if indicated], urinalysis, spot urine, and immunogenicity (presence of binding antibodies specific to CSL112 and apoA-I).
Pharmacokinetics	Blood samples will be collected for assessment of plasma apoA-I and PC concentrations.
CCI	[redacted]
Other Assessments	Blood samples will be collected and stored for possible future virology assessment and analysis of emerging pathogens. Analysis of the stored virology sample will only be done if consent is obtained from the study subject.
Statistical Analyses	**Safety Analyses**: All subjects who received at least a partial infusion of investigational product (CSL112 or placebo) will be evaluated for safety. Treatment group classification will be according to the treatment actually received. Adverse events (AEs) will be summarized by treatment, grade, relatedness, and seriousness. Changes from baseline (ie, pre-infusion on Study Day 1) in clinical laboratory assessments, vital sign measurements, ECG interval measurements, and immunogenicity will be summarized by treatment and the clinical significance of the changes will be assessed. Descriptive statistics will be used to summarize the exposure to the investigational products and the safety assessments.

For the co-primary safety endpoints of treatment-emergent renal SAEs and AKI rates, incidence rates will be based on the number of subjects with at least 1 occurrence of the event of interest; that is, a subject with 2 treatment-emergent renal SAEs or 2 instances of AKI will be counted once. The difference in incidence rates will be computed by subtracting the rate in the placebo arm from the incidence rate in the CSL112 arm so that a positive difference indicates a higher incidence rate in the CSL112 arm. For each co-primary endpoint, Newcombe-Wilson 2-sided 95% confidence intervals around the difference in incidence rates will be calculated if at least 1 event occurs. Otherwise, an exact, 1-sided, upper 97.5% confidence interval will be reported for the incidence rate in each treatment arm.

PK CCI **Analyses**: Measured plasma concentrations of apoA-I and PC, and baseline-corrected concentrations (ie, change from baseline) will be listed and summarized by time point. Plasma PK parameters for apoA-I and PC will be summarized descriptively. The following parameters will be calculated:

- Maximum concentration in plasma (C_{max})
- Accumulation Ratio

Nonlinear mixed effects modeling will be performed to assess the PK data for apoA-I and PC. This population-based approach will be used to explore and quantify clinically relevant covariates such as age, sex, and renal function on population PK parameters.

CCI

Safety Reviews

An external program level DSMB will independently evaluate safety data during the conduct of the study.

In order to ensure that a safety signal has not emerged that would affect the conduct of the study, the DSMB will review safety data after every 6 subjects have received 2 infusions of investigational product and have pre-infusion safety data available before the third infusion at Visit 5. These reviews will continue until at least 60 subjects (approximately 75% of subjects) complete Visit 5. In addition, the independent DSMB will have interim safety reviews when: (1) approximately 25% of subjects have completed the Active Treatment Period (Visit 7), (2) approximately 50% of subjects have completed Visit 5, and (3) approximately 50% of subjects have completed the Active Treatment Period (Visit 7). If any of the safety criteria as specified in the DSMB charter are met at these reviews, continuation of the study without alteration should be

	questioned as it may be an early indication of an unacceptable safety profile in the broader population. The DSMB may recommend a change to the protocol to ameliorate any safety concerns or provide recommendations regarding subsequent dosing and/or study progression/stopping. The DSMB will also be convened to review all available data if 1 or more of the study stopping rules is met (see Section 3.6.2).

Schedule of Assessments

Study Period	Screening[a]	Active Treatment Period														Safety Follow-up
Visit #	1	2			3	4			5			6			7	8
Study Day(s) (range)	(-5 to -1)[b]	1			2 (+1)	8 (+3)			15 (+3)			22 (+3)			29 (+3)[f]	60 (+7)
Infusion #		1[c, d]				2[c, e]			3[c, e]			4[c, e]				
Time relative to infusion		Before infusion/ Baseline	SOI (0 h)	EOI	24 to 48h post SOI (±6h)	Before infusion	SOI	EOI	Before infusion	SOI	EOI	Before infusion	SOI	EOI		
ADMINISTRATIVE PROCEDURES																
Informed Consent	X															
Medical and Surgical History	X															
Demography	X															
(Prior) Concomitant Medications Review	X	X			X	X			X			X			X	X
Inclusion & Exclusion Criteria	X	X														
IRT Subject Registration, eGFR Calculation and Randomization[g]	X	X														
CLINICAL PROCEDURES/ ASSESSMENTS																
Height	X															
Body weight	X														X	X
ECG (12-Lead)	X	X													X	X
Physical Examination	X														X	X
Vital Signs[h]	X	X		X	X	X		X	X		X	X		X	X	X
Hypovolemia Assessment[i]		X				X			X			X				
Investigational Product Infusion[c,d,e]			X[d]				X[e]			X[e]			X[e]			
Infusion Site Assessment[j]		X		X	X	X		X	X		X	X		X		
Bleeding Event Assessment[k]		X			X	X			X			X			X	X
Drug Hypersensitivity Assessment[l]				X				X			X			X		
AE Assessment[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening[a]	Active Treatment Period														Safety Follow-up
Visit #	1	2			3	4			5			6			7	8
Study Day(s) (range)	(-5 to -1)[b]	1			2 (+1)	8 (+3)			15 (+3)			22 (+3)			29 (+3)[f]	60 (+7)
Infusion #		1[c, d]				2[c, e]			3[c, e]			4[c, e]				
Time relative to infusion		Before infusion/ Baseline	SOI (0 h)	EOI	24 to 48h post SOI (±6h)	Before infusion	SOI	EOI	Before infusion	SOI	EOI	Before infusion	SOI	EOI		
LABORATORY PROCEDURES/ ASSESSMENTS																
Urine Pregnancy Test[n]	X														X	X
FSH Measurement (central lab)[o]	X															
Serum Biochemistry (central lab)	X	X			X	X			X			X			X	X
ALT, Total Bilirubin, Serum Creatinine (local lab)[p]	X	X			X	X			X			X				
CCI		X			X	X						X			X	
Hematology (central lab)[q, r]		X		X[q]	X[q]	X			X			X			X	X
Urinalysis	X[s]	X			X	X			X			X			X	
CCI		X			X	X			X			X			X	
Archival Urine Sample		X			X	X			X			X			X	
Virology Sample Collection[t]		X													X	X
Immunogenicity Testing[u]		X													X	X
PK Sampling[v]		X		X	X							X		X		
CCI		X		X	X									X		
CCI		X		X	X									X		
CCI		X			X										X	X
CCI		X		X	X	X			X			X			X	X
Archival Blood Sample[z]		X													X	X

AE = adverse event; ALT = alanine aminotransferase; AMI = acute myocardial infarction; apoA-I = apolipoprotein A-I; CCI B; BARC = Bleeding Academic Research Consortium; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CV = cardiovascular; DSMB = Data and Safety Monitoring Board; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EOI = End of

Infusion; FMC = first medical contact; FSH=follicle stimulating hormone; h = hour; CCI ; IV= intravenous; IRT = interactive response technology; Lab =laboratory; CCI ; mRNA = messenger ribonucleic acid; CCI ; PC = phosphatidylcholine; CCI PEG= polyethylene glycol; PK = pharmacokinetic; SAE = serious adverse event; SOI = Start of Infusion; ULN = upper limit of normal; WBC = white blood count.

a. Screening and randomization of subjects may occur on the same day (Study Day 1 of the Active Treatment Period) provided that the minimum time after FMC for the index AMI or after administration of IV contrast agent is adhered to so renal function stability is assessed before administration of the first infusion of investigational product (Sections 8.2.1.2 and 8.2.2.1). **All procedures and assessments specified at Visit 1 and Visit 2 before infusion baseline must still be performed if screening and randomization are conducted on the same day**. If Visits 1 and 2 combined, there may be a single blood draw for central laboratory serum biochemistry, and local laboratory ALT, total bilirubin, and serum creatinine. Both a local laboratory and central laboratory urinalysis should be performed. There may be 1 ECG. Single assessments of vital signs, concomitant medications, and AEs are also acceptable.

b. Depending on time of event and time required from evaluation in the Emergency Department, cardiac catheterization laboratory administration of contrast dye and assessment of renal and hepatic function screening duration up to and including randomization must occur within 5 days of FMC for the index AMI.

c. Investigational product will be infused intravenously over 2 hours. Time zero (0 hours) is at the start of the first infusion; all times thereafter are relative to time zero, the start of the first infusion. If the infusion is interrupted for any reason, the total duration of the infusion should not exceed 3 hours. The infusion of investigational product may occur in the hospital or in the outpatient setting. Doses of investigational product should be administered 7 to 10 days apart, with all 4 infusions administered within 30 days from Study Day 1 (Visit 2).

d. Before the first infusion of investigational product, all subjects must be clinically stable, have hepatic function tests within acceptable limits, and have evidence of stable renal function at least 12 hours after FMC for the index event. For subjects who undergo angiography, stable renal function is defined as a serum creatinine value obtained at least 12 hours after contrast administration that is increased < 0.3 mg/dL from the pre-contrast administration value (Table 7).

e. Ongoing eligibility for all subsequent infusions of investigational product will be confirmed before administration of each subsequent infusion and will be based on the criteria presented in Section 8.2.2.2, Table 8. An infusion may be skipped or delayed at the discretion of the Investigator if more time is necessary to confirm renal function stability or to evaluate and treat an AE, before the next infusion (Section 8.2.2.2). If an infusion is skipped or delayed for a medical or safety reason, the medical monitor should be contacted for further guidance.

f. Visit 7 must be at least 7 (+3) days after the fourth infusion of investigational product. However, depending on the actual timing of the 4 infusions, Study Day 29 could occur between 28 to 40 days after the first infusion.

g. Interactive response technology (IRT) is used to1) assign a subject identification number at Visit 1, and 2) automatically calculate eGFR (based on the subject's age, sex, race, and serum creatinine) and randomize eligible subjects at Visit 2. The serum creatinine used for IRT eGFR calculation should be the local laboratory value at Visit 2. Steps 1 and 2 can be completed at a single visit if screening and randomization occurs on the same day (Section 8.2.1.2).

h. Vital signs include blood pressure (systolic and diastolic) after the subject has rested in a sitting or supine position ≥ 5 minutes, pulse rate (per minute), and body temperature (using oral or tympanic measurement). (Note that body weight is measured separately and not each time that vital signs are to be assessed.)

i. Before starting an infusion of investigational product, the Investigator or a medically qualified delegate should assess each subject for presence of hypovolemia. This assessment may include assessment of dry mouth, skin tenting, orthostasis, dizziness, etc. If hypovolemia is suspected or confirmed, the Investigator or a medically qualified delegate should administer IV replacement fluid as clinically indicated. During the infusion, subjects should be encouraged to drink fluids. Before departing from the clinic and after completion of the infusion and all other study assessments, all subjects should be asked to void. If a subject is unable to void before leaving the clinic, he/she should be contacted at home to determine whether or not they have been able to void.

j. Any abnormal finding at the investigational product infusion site, including bruising, redness and/or swelling should be recorded as an AE. Bruising should be assessed using the BARC criteria (Appendix IV).

k. Bleeding events will be assessed according to the BARC definition for bleeding (see Appendix IV). The eCRF page for bleeding assessments must be completed for each suspected bleeding event. Bleeding events should be reported as AEs.

l. All subjects will be observed for hypersensitivity reaction for at least 1 hour after the end of the first and second infusions of investigational product. Observation for hypersensitivity reaction for at least 1 hour after the third and fourth infusions of the investigational product is under the clinical discretion of the Investigator. If a serious drug hypersensitivity reaction is suspected, assessments should be performed as per Section 8.2.3.6.

m. Reporting of bleeding events and renal SAEs includes completion of the Bleeding Event eCRF page or Renal SAE eCRF page, respectively, with supporting documentation (hospital records and tests).

n. Required for all women of child-bearing potential.

o. To be assessed only for amenorrheic females between the ages of 45 and 60 years to document that the subject is not of child-bearing potential.

p. Local laboratory blood samples for serum creatinine, ALT, and total bilirubin will be used to assess for study eligibility (including determination of renal function based on eGFR using the CKD-EPI equation (Section 4.1.1) and safety for continued administration of investigational product (Section 8.2.2.2). Results must be reviewed by the Investigator before infusions on Study Days 1, 8, 15, and 22. The sample may be obtained up to 48 hours before infusions 2, 3, and 4. **For all time points at which a local laboratory value is collected, a sample should also go to the central laboratory for analysis.** If ALT is elevated to > 3 x ULN with a concomitant elevation in total bilirubin to >2 x ULN **OR** if ALT is elevated to > 5 x ULN, additional assessments should be performed per Section 8.1.2, Table 4.

q. Blood sample to be collected for WBC differential count alone at these time points CCI [redacted]

r. If a decrease in hemoglobin post-infusion that is ≥ 2 g/dL from baseline is observed and is not explained by overt blood loss, then repeat hemoglobin and additional assessments should be obtained (see Section 8.2.3.7.2). Hemolysis should also be considered if total bilirubin > 2 x ULN is observed.

s. At screening only, urinalysis will be performed by local laboratory urine dipstick. If dipstick demonstrates high grade proteinuria, a urine sample should be sent to the central laboratory for urinalysis. For all other visits, a urine sample will be sent to the central laboratory for urinalysis.

t. Virology samples will be collected and stored for 1 year after completion of the clinical study report for possible future assessment of currently unspecified viral agents (assessment to occur only if required and after additional consent is obtained from the subject).

u. Immunogenicity testing includes serum antibodies to CSL112 and apoA-I.

v. Blood samples for PK will be analysed for plasma concentrations of apoA-I and PC.

w. CCI [redacted]

x. CCI [redacted]

y. [redacted]

z. Blood samples will be collected and stored. Analysis will be directed by the Steering Committee and based on the latest available information on the utility of such measurements.

NOTE: Assessments are to be conducted at all times and days marked with an X.

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List of Abbreviations

Abbreviation	Definition
ACS	Acute coronary syndrome
AE(s)	Adverse event(s)
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
apoA-I	Apolipoprotein A-I
CCI	[redacted]
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum plasma concentration
CRP	C-reactive protein
CSLB	CSL Behring LLC
CSL112	Company code name for reconstituted high density lipoprotein
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DSMB	Data and Safety Monitoring Board
ECG(s)	Electrocardiogram(s)
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOI	End of infusion
FDA	Food and Drug Administration
FMC	First medical contact

FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
h	hour(s)
CCI	[redacted]
hs	High sensitivity
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig(A, G, E, or M)	Immunoglobulin (A, G, E, or M)
IGIV	immune globulin intravenous
CCI	[redacted]
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
CCI	[redacted]
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mRNA	Messenger ribonucleic acid
NOAEL	No observed adverse effect level
CCI	[redacted]
NYHA	New York Heart Association
PC	phosphatidylcholine
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRBCs	Packed red blood cells

PT	Preferred Term
RBC	red blood cell
RI	Renal impairment
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standard MedDRA query
SOI	Start of infusion
TEAE	Treatment-emergent adverse events
ULN	Upper limit of normal
w / v	Weight per volume
WBC	White blood cell
WFI	Water for Injection

1. INTRODUCTION

1.1 BACKGROUND INFORMATION ON CSL112

1.1.1 Overview

Acute coronary syndrome (ACS) is a life-threatening condition, that 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 (UA), a myocardial infarction (MI [ie, 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 cardiovascular (CV) events can be as high as 20% per year (Fox et al, 2006), and are inversely related to renal function status, such that subjects with mild, moderate, and severe renal impairment (RI) have progressively poorer long-term prognosis as compared with patients with normal renal function (Gibson et al, 2004; Fox et al, 2010). In patients with ACS and RI, the prognosis, both short- and long-term, is worse than for those with normal renal function, as the risk of CV events and mortality is inversely proportional to the estimated glomerular filtration rate (eGFR [Nabais et al, 2008; Bhandari and Jain, 2012]). Therefore, the identification of therapies that are safe and effective in patients with concurrent RI and ACS would represent an important advancement in medical therapy.

Renal impairment is a prevalent and growing concurrent condition in ACS and acute myocardial infarction (AMI). Among 13,307 patients who participated in the Non-ST-Segment Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction (NSTE-ACS TIMI) trials, 37.2% of patients had normal renal function (GFR $\geq$ 90 mL/min/1.73 m^2), 47.1% of patients had mildly impaired GFR (GFR $\geq$ 60 to $<$ 90 mL/min/1.73 m^2), and 15.1% of patients had moderately impaired GFR (GFR $\geq$ 30 to $<$60 mL/min/1.73 m^2 [Gibson et al, 2004]). In a more recent analysis of 49,491 AMI patients from the US-based National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry, which collects data from 280 hospitals for all

patients with a primary diagnosis of MI (either non-ST segment elevation myocardial infarction [NSTEMI] or ST segment elevation myocardial infarction [STEMI]) who presented within 24 hours of the onset of an ischemic syndrome, approximately 30.5% of patients had Stage 3 chronic kidney disease (CKD, ie, moderate RI [Fox et al, 2010]). Given the growing prevalence of RI in patients with AMI coupled with the subsequent heightened risk of recurrent CV events in this population, identification of therapies that are safe and effective in these patients is critical.

High density lipoprotein (HDL) cholesterol exerts a protective effect in experimental models of atherosclerotic CV disease. The proposed mechanism(s) for the atheroprotective properties of HDL are multifaceted (Remaley et al, 2008; Tardif et al, 2009). High density lipoprotein is believed to bring about beneficial effects mainly by reverse cholesterol transport, whereby excess cholesterol is removed from arteries containing atherosclerotic plaques 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).

CSL112 is a novel formulation of apoA-I purified from human plasma and reconstituted to form HDL particles. It is being developed for use in patients with AMI for the reduction in risk of recurrent CV events via the action of apoA-I. Apolipoprotein A-I is the active component of CSL112 and other components include phosphatidylcholine (PC), sodium cholate, and sucrose. Additional information about the disposition of components of administered CSL112 can be found in the Investigator's Brochure (IB) for CSL112.

1.1.2 Nonclinical Evaluation

CSL112 single and repeat dose nonclinical safety studies have been conducted. After a single intravenous (IV) infusion of 1-hour duration, a no observed adverse effect level (NOAEL) of 300 mg/kg was established in both the rat and cynomolgus monkey. In the repeat dose studies (CSL112 administered once every 3 days for 4 weeks by 2-hour IV infusion), a NOAEL of 80 mg/kg was established in the rat; however, a NOAEL was not established in the

cynomolgus monkey because some adverse effects were observed at the lowest dose tested (80 mg/kg). No treatment-related deaths occurred in any of the toxicity studies.

After IV administration 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.

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

1.1.3 Previous Clinical Experience

CSL112 has been evaluated in 2, single center, randomized, placebo-controlled, phase 1, healthy adult, non-Investigational New Drug (IND) studies conducted in Australia (CSLCT-HDL-09-63 – Single Ascending Dose [SAD] study; CSLCT-HDL-10-68 – Multiple Ascending Dose [MAD] study) and 1 multicenter center, double-blind, placebo-controlled, ascending single-dose phase 1 non-IND study in adult subjects with moderate RI (eGFR ≥ 30 and < 60 mL/min/1.73 m^2) and in healthy adult subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) (Study CSL112_1001) conducted in Germany and the United Kingdom. Study CSL112_1001 was initiated in the second quarter of 2015, enrolment was completed as of 16 November 2015, and last subject last visit occurred on 15 February 2016. This study was conducted to investigate the pharmacokinetic (PK), safety, and tolerability of CSL112 in adult subjects with moderate RI and in age, gender, and weight matched healthy adult subjects with normal renal function. The primary objective of the study was to assess the effect of moderate RI on the PK of CSL112. Subjects were randomized 3:1 active to placebo within a cohort (4 cohorts total: 2 moderate RI and 2 healthy adult subject cohorts at 2 different doses, each with 8 subjects). Twenty-four subjects received 1 infusion of CSL112 in this study, 12 with normal renal function and 12 with moderate RI. Based on Data and Safety Monitoring (DSMB) review of PK and safety data from 12 moderate RI subjects receiving

either the CSL112 2 g or 6 g dose, the 6 g dose has been selected for the current study. Data from the Active Treatment Period are available and demonstrate an acceptable safety profile of a single dose of CSL112 in adult subjects with moderate RI (Section 1.3). The rationale for the 6 g CSL112 dose based on PK data from this phase 1 study is presented in Section 3.2.

In addition, a phase 2a IND study (CSLCT-HDL-10-70a) has been conducted in subjects diagnosed with stable atherothrombotic disease; in essence, the AMI target population after their initial acute presentation. The phase 2a subjects 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) and were stratified by renal function (ie, normal renal function or mild RI). The goals of the phase 2a study were to evaluate the comparability of the PK and safety profile in patients with stable atherothrombotic disease as compared to that of healthy adults and to evaluate a range of doses to be administered in future CSL112 clinical studies in AMI patients who are at high risk of subsequent CV events.

A total of 126 subjects (93 healthy adults, including 12 with moderate RI, and 33 patients) have received at least 1 dose of CSL112 in 4 completed studies. The results of the phase 1 and 2a studies showed acceptable safety, PK, and pharmacodynamic (PD) profiles of CSL112 across a range of doses and renal function groups.

A phase 2b study (Study CSLCT-HDL-12-77) was initiated in the third quarter of 2014 and completed in the first quarter of 2016. It is a multicenter, randomized, placebo-controlled study to investigate the hepatic and renal safety and tolerability of multiple dose administration of 2 IV infusion regimens of CSL112 (low [2 g] and high dose [6 g]) versus placebo in approximately 1200 subjects with acute myocardial infarction (AMI). Subjects are stratified by renal function (normal renal function [eGFR $\geq$ 90 mL/min/1.73 m^2] or mild RI [eGFR $\geq$ 60 and $<$ 90 mL/min/1.73 m^2]). The study consisted of a Safety Lead-in Period, during which subjects received a single 2-hour infusion of CSL112 (2 g) or placebo, followed by the main study, during which subjects receive four 2-hour infusions of investigational

product (CSL112 low [2 g] or high dose [6 g] or placebo), a minimum of 7 days apart, during the 4-week Active Treatment Period. The data from the Safety Lead-in Period were evaluated by the program level DSMB on 9 January 2015 and enrolment of subjects into the main study began in January 2015. Enrolment in the main study completed as of 15 November 2015 and the last subject last visit occurred on 21 March 2016. Based on a randomization ratio (CSL112:placebo) of 2:1 and final enrolment of 1258 randomized subjects, approximately 839 subjects will have received at least 1 infusion of CSL112 in the phase 2b study. To date, the program level DSMB has reviewed safety and PK data from the Active Treatment Period after 5%, 10%, 25%, 50%, and 75% of subjects were enrolled, and have recommended the study to continue without change. Data are not yet available for this study. Further details regarding the phase 2 study may be found in the IB for CSL112.

Thus, as of 16 November 2015, approximately 965 subjects have received at least 1 infusion of CSL112 in completed studies of the CSL112 clinical development program.

1.2 STUDY OVERVIEW

CSL112 drug product resembles nascent HDL. It is a novel formulation of apoA-I, PC, and cholate; and is stabilized by sucrose. CSL112 is being developed for the reduction of recurrent CV events after AMI. The premise of the CSL112 mechanism of action and the resulting treatment strategy is that infusion of apoA-I after the index AMI event, and during the subacute period after the event, will reduce the size and/or instability of atherosclerotic plaque, thereby reducing the risk of plaque rupture or erosion that would lead to a recurrent CV event in patients with AMI.

Renal impairment (RI) is a prevalent and increasingly common concurrent condition in patients with AMI. Patients who experience an AMI event are at high risk for a recurrent CV event and mortality is inversely related to renal function status: subjects with mild, moderate, and severe RI have, respectively, progressively poorer long-term prognosis as compared with patients with normal renal function. As the number of AMI patients with RI is relatively high (~15% to 30%) (Gibson et al, 2004; Fox et al, 2010), the identification of therapies that are

safe and effective in these patients would represent an important advancement in medical therapy.

This study is a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group, study to investigate the safety and tolerability of up to 4 weekly IV administrations of CSL112 compared with placebo in subjects with moderate RI (eGFR ≥ 30 and < 60 mL/min/1.73 m^2) and AMI.

CSL112 drug product 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 intravenous (IGIV) products formulated with sucrose were administered at high doses or high rates of administration (Epstein and Zoon, 2000). Thus, evaluation of the renal safety of CSL112 is warranted, specifically in the subpopulation of patients with moderate RI who have experienced a recent AMI event. Although no renal safety concerns were identified in the completed CSL112 phase 1 and 2a studies (n=126 total subjects treated with CSL112: 96 with normal renal function, 15 with mild RI, and 15 with moderate RI), further evaluation is warranted before the inclusion of AMI patients with moderate RI in a phase 3 morbidity and mortality outcomes trial.

This study is intended to characterize the renal risk profile in subjects with moderate RI who have experienced a recent AMI. The occurrence of clinically important renal serious adverse events (SAEs) as reported by the Investigator and AKI, defined as an increase in serum creatinine of ≥ 0.3 mg/dL (26.5 µmol/L) from baseline that is sustained upon repeat measurement, will be evaluated. In subjects with moderate RI who have undergone percutaneous coronary intervention (PCI), the occurrence of AKI as defined by the Acute Kidney Injury Network (AKIN) criteria is approximately 10% (Tsai et al, 2014). After excluding subjects with evidence of AKI at screening, the effect of 4 weekly infusions of CSL112 or placebo on the incidences of renal SAEs and AKI will be evaluated in this study of post-AMI moderate RI patients.

1.3 POTENTIAL RISKS AND BENEFITS

The Development Core Safety Information document (appended to the IB for CSL112) outlines the potential risks to subjects administered CSL112 and precautions for its use.

The most frequently reported AEs in completed clinical studies of CSL112 included: Infusion Site Pain, Infusion Site Swelling, Infusion Site Induration, Infusion Site Erythema, Infusion Site Coldness, Injection Site Phlebitis, Catheter Site Phlebitis, Infusion Site Haematoma, Injection Site Haematoma, Vessel Puncture Site Haematoma, and Vessel Puncture Site Haemorrhage. Headache was also frequently reported in these studies. Events related to injection or infusion site reactions, local tolerability events related to bruising (coded to a Preferred Term [PT] Haematoma in the Medical Dictionary for Regulatory Activities [MedDRA]), and Headache were reported more frequently in subjects who received CSL112 as compared with placebo. Most of these events were mild and transient. Adverse events (AEs) reported within other System Organ Classes (SOCs) occurred with similar frequency in the placebo and active treatment groups across the 4 completed CSL112 studies. No renal safety concerns were identified in the completed CSL112 phase 1 or 2a studies.

A thorough panel for renal assessment has been integrated into the current study, as CSL112 contains sucrose as a stabilizer, and administration of sucrose IV has been associated with reports of AKI attributed to osmotic nephrosis when IGIV products formulated with sucrose were administered at high doses or at high rates of administration. The highest dose of sucrose administered in the completed phase 2a study in patients with stable atherothrombotic disease and normal renal function or mild RI did not exceed the lowest dose published in the literature associated with potential nephrotoxicity (Anderson and Bethea, 1940). CSL112 has been reformulated such that the maximum dose of sucrose to be administered in this study is approximately 2.5-fold less than this 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 hour (50 mg/min) ensures a sucrose infusion rate of ≤ 1.7 mg sucrose/kg/min for a 50-kg adult, which is well within the published

guideline for safe administration of sucrose containing IGIV products (Epstein and Zoon, 2000).

In the completed phase 1 and 2a clinical studies with CSL112, no clinically significant elevations (> 3 x upper limit of normal [ULN]) in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) have been reported in 126 subjects who have received CSL112. One subject treated with a single 135 mg/kg dose of CSL112 in the SAD study experienced a transient elevation in total bilirubin > 2 x ULN at a single time point. No AEs were reported in association with this laboratory finding. Two subjects with moderate RI treated with CSL112 6 g in Study CSL112_1001 had treatment-emergent non-serious AEs of "Blood Bilirubin Increased" for transient elevations at a single time point on Study Day 2 (maximum of 1.16 x ULN). One subject with normal renal function treated with CSL112 6 g in Study CSL112_1001 had an elevation in total bilirubin to > 1.5 x ULN but less than 2 x ULN at a single time point on Study Day 2 that was not reported as a treatment-emergent AE (TEAE). In the phase 2b study (Study CSLCT-HDL-12-77), 2 reports of serious liver dysfunction (Liver Disorder and Hepatic Function Abnormal) have been received as of 2 May 2016. Each event was assessed as related to investigational product by the Investigator. Both cases demonstrated a mixed cholestatic and hepatocellular picture, and neither subject was considered as meeting Hy's Law criteria. These cases were reviewed by the DSMB immediately after they were reported, and the DSMB determined that the study may continue without modification. A thorough panel for hepatic assessment has also been incorporated into the protocol and the study will be conducted under oversight by the program level DSMB.

No SAEs were reported in the SAD or MAD phase 1 studies and no SAEs were reported in the phase 2a study in subjects who received CSL112.

In Study CSL112_1001, 2 subjects with normal renal function who received CSL112 6 g experienced a total of 2 SAEs during the Active Treatment Period that were not related to investigational product (pain in right shoulder [due to loosened osteosynthesis plate], injury

of right meniscus). There were no deaths and no subject discontinued from the study because of a TEAE.

In the phase 2b study (Study CSLCT-HDL-12-77), as of 2 May 2016, 4 SAEs were reported for 4 subjects as related to investigational product by the Investigator (Pharyngeal Oedema [1 subject], Hepatic Function Abnormal [2 subjects], Gastrointestinal Haemorrhage [1 subject]). Eight subjects had 18 SAEs with a fatal outcome and were assessed as not related to investigational product by the Investigator (Pneumonia, Acute Respiratory Failure, Cardiac Arrest, Pneumothorax, Chronic Obstructive Pulmonary Disease, Hypoxic Ischemic Encephalopathy; Septic Shock; Basal Ganglia Haemorrhage; Cerebral Haemorrhage, Brain Metastatic Cancer; Cardiac Failure [2 events]; Shock Haemorrhagic, Multiple Organ Dysfunction Syndrome; Cardiac Aneurysm, Pulmonary Embolus, and Death). On 21 December 2015, based on review of safety and PK data after 75% of subjects had completed the Active Treatment Period, the program level DSMB determined that there were no significant safety or PK concerns and recommended that the study continue under the current protocol without modification.

The risk of viral and prion contamination is a feature common to all biologic agents where the manufacture involves the use of materials of animal or human origin. CSL112 may carry a risk of transmitting infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease agent) because it is made from human blood. 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 virus inactivation / removal steps in the manufacturing process.

There is potential for allergic reactions or hypersensitivity to CSL112 in certain individuals, given the constituents of the product. CSL112 consists of apoA-I isolated from human plasma that 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 addition, study level stopping rules will provide guidance if there are occurrences of serious drug hypersensitivity AEs.

It is the central premise of the CSL112 program that infusion of apoA-I via reconstituted HDL will provide therapeutic benefit to patients with AMI. Based on the previous clinical data, the dose of CSL112 selected for use in this study should raise cholesterol efflux capacity by a meaningful amount. The increase in cholesterol efflux capacity of blood plasma may enable the acceptance of excess cholesterol from atherosclerotic plaque. The resulting reduction in plaque cholesterol should render the plaques more stable and less likely to rupture. This and other purported apoA-I related actions may translate to a reduction in the subacute risk of cardiac ischemia and recurrent CV events in patients with AMI.

Thus, the associated benefit risk assessment of the study is acceptable for subjects enrolled in the study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE AND ENDPOINT

2.1.1 Primary Objective

The primary objective of this study is to assess the renal safety of CSL112 in subjects with moderate RI and AMI after administration of up to 4 weekly infusions of CSL112.

2.1.2 Co-primary Endpoints

The renal safety profile of CSL112 in subjects with moderate RI and AMI who receive up to 4 weekly administrations of CSL112 will be assessed by co-primary endpoints of the incidences of treatment-emergent (1) renal SAEs as defined below, and (2) AKI, defined as an absolute increase in serum creatinine from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period that is sustained upon repeat measurement by the central laboratory no earlier than 24 hours after the elevated value. If no repeat value is obtained [due, for

example, to loss of follow-up or protocol violation], a single serum creatinine value that is increased from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period would also fulfil the definition of AKI.

Treatment-emergent is defined as occurring at or after the start of the first infusion. Baseline for determination of AKI is defined as the pre-infusion central laboratory serum creatinine level on Study Day 1.

A renal SAE is defined as any SAE with a MedDRA PT included in the Acute Renal Failure **narrow** Standard MedDRA Query (SMQ) or a PT of Renal Tubular Necrosis, Renal Cortical Necrosis, Renal Necrosis, or Renal Papillary Necrosis.

Incidence rates will be based on the number of subjects with at least 1 occurrence of the event of interest; that is, a subject with 2 treatment-emergent renal SAEs or 2 instances of AKI will be counted once.

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

2.2.1 Secondary Objective(s)

The secondary objectives of the study are:

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

2.2.2 Secondary Endpoints

Secondary safety and tolerability endpoints include:

1. The occurrence of any TEAEs throughout the study.

2. The occurrence of treatment-emergent adverse drug reactions or suspected adverse drug reactions defined as:
    a. All TEAEs, including local tolerability events, that begin during or within 1 hour after the end of an infusion, or
    b. Those TEAEs which the Investigator or Sponsor indicate may be causally related to the administration of the investigational product (CSL112 or placebo), or
    c. All TEAEs for which the Investigator's causality assessment is missing or indeterminate, or
    d. All TEAEs for which the incidence in an active treatment arm exceeds the exposure-adjusted incidence rate in the placebo arm by 30% or more, provided the difference in incidence rates is 1% or more.
3. Changes from baseline (ie, pre-infusion on Study Day 1) through to the end of the Active Treatment Period in renal status defined as:
    a. Absolute increases from baseline in serum creatinine as follows:
        i. ≤ baseline value
        ii. > 0 to < 0.3 mg/dL
        iii. ≥ 0.3 to ≤ 0.5 mg/dL
        iv. > 0.5 mg/dL
    b. Increases in serum creatinine that are sustained for ≥ 24 hours upon repeat measurement as follows:
        i. ≥ 1.5 x baseline values
        ii. ≥ 2 x baseline value
        iii. ≥ 3 x baseline value
        iv. serum creatinine ≥ 4.0 mg/dL (353.6 µmol/L)
    c. Initiation of renal replacement therapy
    d. Decrease in eGFR by ≥ 25% from baseline starting during the Active Treatment Period and that is sustained at the final study visit

4. Change from baseline (ie, pre-infusion on Study Day 1) in hepatic status that occurs during the Active Treatment Period and that is sustained for ≥ 24 hours upon repeat measurement as follows:
   a. ALT > 3 x ULN
   b. ALT > 5 x ULN
   c. ALT > 10 x ULN
   d. Serum total bilirubin > 1.5 x ULN (Note: For subjects with a history of Gilbert's syndrome, this assessment will be based on indirect bilirubin.)
   e. Serum total bilirubin > 2 x ULN (Note: For subjects with a history of Gilbert's syndrome, this assessment will be based on indirect bilirubin.)
   f. Possible Hy's Law cases, as defined in the FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009; see Section 9.1.3.3 for definition of Hy's Law).
5. The occurrence of treatment-emergent bleeding events as defined by the Bleeding Academic Research Consortium (BARC) criteria (Mehran et al, 2011) from the start of the first infusion until the end of the Safety Follow-up Period.
6. Clinically significant changes in clinical laboratory tests results (serum biochemistry, hematology, and urinalysis), physical examinations findings, body weight, electrocardiograms (ECGs), and vital signs (blood pressure, pulse rate, and body temperature).
7. The occurrence of binding antibodies specific to apoA-I and/or CSL112.

Secondary PK endpoints include:

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

2.3 CCI [redacted]

2.3.1 CCI [redacted]

CCI [redacted]

2.3.2 CCI [redacted]

CCI [redacted]

3. STUDY DESIGN

3.1 STUDY DESIGN AND RATIONALE

This is a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and tolerability of up to 4 weekly IV administrations of 6 g CSL112 compared with placebo in subjects with moderate RI and AMI. The 6 g CSL112 dose was selected after DSMB review of safety and PK data from the ongoing phase 1 PK and safety

study in subjects with moderate RI (Study CSL112_1001). Details regarding the rationale for dose selection are outlined in Section 3.2.

The main study will enrol approximately 81 subjects who will be randomly assigned in a 2:1 ratio to receive infusions of 6 g CSL112 (54 subjects) versus placebo (27 subjects) to evaluate safety. To ensure that at least one-third of the study population has an eGFR in the CKD stage 3b range (eGFR 30 to < 45 mL/min/1.73 m^2), no more than two-thirds of the study population (ie, 54 subjects) will have an eGFR in the CKD 3a range (45 to < 60 mL/min/1.73 m^2). Randomization will be stratified by eGFR (30 to < 45 mL/min/1.73 m^2 or 45 to <60 mL/min/1.73 m^2) as calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) equation (Levey et al, 2009; Stevens et al, 2010), and by medical history of diabetes requiring current treatment with any anti-diabetic medication (yes or no). Clinical procedures for these subjects will include assessments for safety (including renal and hepatic), PK, CCI [redacted] CCI [redacted] CCI [redacted]

The study will consist of screening and 2 study periods: an Active Treatment Period during which patients will receive 4 IV infusions of investigational product (ie, CSL112 or placebo) over approximately 29 days and a Safety Follow-up Period (approximately 30 days from the Active Treatment Period) (Figure 1). A summary of study assessments and procedures by visit is shown in the Schedule of Assessments.

Subjects will be assessed for eligibility at screening and before randomization (Visit 1 and Visit 2 before infusion). The screening period up to and including randomization must occur within 5 days of first medical contact (FMC) for the index AMI (Figure 1). Subjects meeting all inclusion criteria and none of the exclusion criteria (Sections 4.1.1 and 4.1.2) will receive

four 2-hour IV infusions of investigational product (6 g CSL112 or placebo), a minimum of 7 days apart, during a 4-week Active Treatment Period. Study assessments for all subjects will be conducted before and after infusions during Visits 2, 4, 5, 6 (Study Days 1, 8, 15, 22), within 24 to 48 hours after the first infusion (Visit 3) and at the end of the Active Treatment Period (Visit 7/Study Day 29). Follow-up safety assessments will be conducted at a final visit (Visit 8) on Study Day 60.

Depending on the time of the index event, time required for evaluation in the emergency department and cardiac catheterization laboratory, administration of contrast agent, and assessment of renal function stability, screening duration may last up to 5 days after FMC for the index AMI. **First medical contact** is defined as the point in time (ie, clock start) at which the subject arrives at the hospital emergency department (ie, door time) or cardiac catheterization laboratory, for evaluation and treatment of AMI. A diagnosis of AMI as per Section 4.1.1 is critical to determining subject eligibility.

Before the first infusion of investigational product, the subject must be clinically stable, have hepatic function test within acceptable limits, and have documented evidence of stable renal function and no suspicion of AKI at least 12 hours after FMC for the index AMI. In addition, for those subjects undergoing angiography with or without PCI, stable renal function, defined as a serum creatinine value that is increased < 0.3 mg/dL (26.5 µmol/L) from the pre-contrast administration value, must be demonstrated at least 12 hours after IV contrast administration (see Section 8.2.2.1, Table 7). The first infusion of investigational product should occur no earlier than 12 hours after FMC or, for subjects undergoing angiography, no earlier than 12 hours after contrast administration. The first infusion should start no later than 5 days after FMC for the index AMI. Within this screening window, earlier administration of the first infusion of investigational product is encouraged.

Screening and randomization of subjects may occur on the same day (Study Day 1 of the Active Treatment Period) provided that the minimum time window after FMC for the index event or administration of IV contrast agent (for subjects undergoing angiography) is adhered

to for assessment of stability of renal function before administration of the first infusion of investigational product (Section 8.2.2.1).

Ongoing eligibility for all subsequent infusions of investigational product will be confirmed before administration of each subsequent dose. Eligibility for continued administration of investigational product will be based on the criteria presented in Section 8.2.2.2, Table 8. Each infusion should be completed as close to the protocol-specified visit schedule as possible, ie, no fewer than 7 days and no more than 10 days between each infusion. An infusion may be skipped or delayed at the discretion of the Investigator if more time is necessary to confirm renal function stability or to evaluate and treat an AE before the next infusion (Section 8.2.2.2). If an infusion is skipped or delayed for a medical or safety reason, the medical monitor should be contacted for further guidance.

Using the maximum interval of 10 days between infusions, the 4 infusions should be administered within 30 days from Study Day 1 (Visit 2). Visit 7 (Study Day 29) must be at least 7 (+3) days after the fourth infusion of investigational product. However, depending on the actual timing of the 4 infusions, Study Day 29 could occur between 28 to 40 days after the first infusion. Where administration of all 4 infusions may exceed the duration of 30 days the medical monitor should be informed for further guidance.

The end of the Active Treatment Period is upon completion of Visit 7 (Study Day 29). The Safety Follow-up Period (approximately 30 days in duration) will begin after Visit 7.

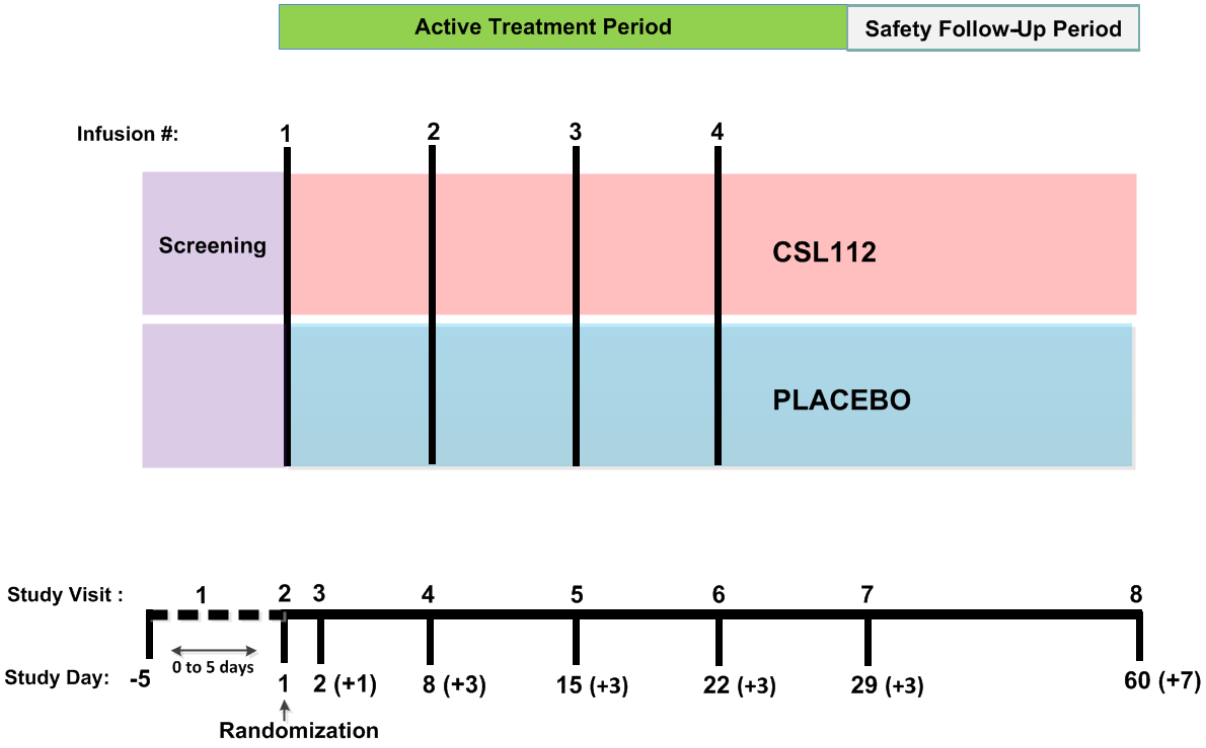
Visit 8 will occur approximately 60 (+7) days after the first infusion and must occur no sooner than 25 days after the last administration of investigational product. Subjects will return to the study clinic and be seen by the Investigator or qualified delegate for study assessments at Visit 8. Adverse events will be assessed at each visit between signing of informed consent and Visit 8.

Subjects who have prematurely discontinued receiving infusion(s) of investigational product should complete an early termination visit (Section 4.1.4). All study assessments to be

performed at the early termination visit should be the same assessments as conducted at Visit 7. Subjects who have discontinued investigational product early should continue to be followed for safety through Visit 8. If the subject cannot be contacted directly to obtain vital status (ie, living or deceased), at a minimum, sites should obtain as much information as possible through telephone contact with healthcare providers, registered mail contact, contact through family or friends or utilization of publically available information.

An external program level DSMB will independently evaluate safety data during the conduct of the study. In order to ensure that an early safety signal has not emerged that would affect the conduct of the study the DSMB will review safety data after every 6 subjects have received 2 infusions of investigational product and have pre-infusion safety data available before the third infusion at Visit 5. These reviews will continue until at least 60 subjects (approximately 75% of subjects) complete Visit 5. In addition, the independent DSMB will have interim safety reviews when: (1) approximately 25% of subjects have completed the Active Treatment Period (Visit 7), (2) approximately 50% of subjects have completed Visit 5, and (3) approximately 50% of subjects have completed the Active Treatment Period (Visit 7). At these reviews the DSMB will assess for any safety signal that has emerged and that would warrant a change in the conduct of the study. The DSMB will also be convened to review all available data if 1 or more of the study level stopping rules is met (see Section 3.6.2).

Figure 1. Study Overview



AMI = acute myocardial infarction; IV = intravenous; FMC = first medical contact
The study will consist of screening and 2 study periods: an Active Treatment Period (approximately 29 days) and a Safety Follow-up Period (approximately 30 days from the end of the Active Treatment Period). Subjects will be assessed for eligibility during screening and up to and including randomization (Visit 1 and Visit 2 before infusion), which may occur no later than 5 days after FMC for the index AMI. Eligible subjects meeting all inclusion criteria and none of the exclusion criteria will receive four 2-hour IV infusions of investigational product (6 g CSL112 or placebo), a minimum of 7 days apart, during a 4-week Active Treatment Period.

3.2 DOSE AND DOSING REGIMEN

CSL112 (6 g) or a matched volume of placebo (0.9% weight/volume [w / v] sodium chloride solution, ie, normal saline) will be administered as a 2-hour IV infusion into a suitable vein (peripheral or central) once weekly for 4 consecutive weeks (4 infusions total).

A 6 g dose of CSL112 has been selected for this study, based upon the DSMB review of safety and PK data from the ongoing phase 1 PK and safety study in subjects with moderate RI (Study CSL112_1001).

Relative to healthy adult subjects in Study CSL112_1001, the baseline levels of apoA-I and PC before CSL112 dosing are comparable in subjects with moderate RI. When adjusted for baseline, the mean PK profiles of apoA-I from the 2 renal function groups overlap substantially. Similarly, the mean PK profiles of PC from the 2 renal function groups also overlapped. Therefore, the comparable exposure between the 2 renal function groups was supported from the PK analysis in Study CSL112_1001. Data from subjects with moderate RI who received CSL112 6 g revealed exposures of apoA-I (mean area under the concentration-time curve [AUC]$_{0\text{-}72}$–5890 mg•h/dL and mean maximum plasma concentration [C_{max}] – 152 mg/dL) and PC (mean $AUC_{0\text{-}24}$ –2420 mg•h/dL and mean C_{max} –208 mg/dL) that were similar to exposures observed in age-, gender-, and weight-matched healthy adults with normal renal function dosed with CSL112 6 g. The corresponding values for adults with normal renal function are: 5140 mg•h/dL for apoA-I $AUC_{0\text{-}72}$, 162 mg/dL for apoA-I C_{max}, 2320 mg•h/dL for PC $AUC_{0\text{-}24}$, and 228 mg/dL for PC C_{max}. In addition, results from Study CSL112_1001 are comparable to those from earlier healthy subject studies (Studies CSLCT-HDL-09-63 and CSLCT HDL 10-68) and those from subjects with stable atherothrombotic disease (Study CSLCT HDL-10-70a). The PK and safety data from the CSL112 6 g cohort in Study CSL112_1001, support the prior DSMB recommendation of 6 g of CSL112 as safe for further evaluation in subjects with moderate RI.

CCI

[redacted]

CCI [redacted]

Based on the safety and PK analyses conducted to date, a 6 g dose administered to subjects with moderate RI is expected to produce apoA-I and PC exposure levels that are similar to those observed in subjects with normal and mild RI.

3.3 PLANNED STUDY DURATION

The maximum duration of the study for an individual subject is expected to be approximately 9 weeks. This estimation is based on:

- A 5-day Screening Period.
- A 4-week Active Treatment Period.
- A 4-week Safety Follow-up Period.

The overall study duration (ie, first subject's screening visit to last subject's end of study visit) will be approximately 9 months.

3.4 PLANNED NUMBER OF SITES

The study is planned to be conducted at approximately 30 sites.

3.5 PLANNED NUMBER OF SUBJECTS

Approximately 81 subjects will be enrolled into this study.

3.6 STUDY MONITORING PROCEDURES

3.6.1 Data and Safety Monitoring Board

The independent program level DSMB will monitor the safe conduct of the study. The DSMB charter outlines the roles and responsibilities of the committee and will guide its operations. The DSMB consists of individuals external to CSL who have relevant clinical trial expertise and experience in safety assessment.

The program level DSMB will:

- Provide recommendations to CSL surrounding study conduct matters that affect safety.
- Review the safety data at the planned interim safety reviews (see Section 10.3.4) and identify if significant safety concerns arise during the study.
- Review all available data if 1 or more of the study level stopping rules is met (see Section 3.6.2)
- Review PK data and any other data that may affect subject or study continuation.
- Make recommendations regarding study progression.

In order to ensure that a safety signal has not emerged that would affect the conduct of the study, the DSMB will review safety data after every 6 subjects have received 2 infusions of investigational product and have pre-infusion safety data available before the third infusion at Visit 5. These reviews will continue until at least 60 subjects (approximately 75% of subjects) complete Visit 5. In addition, the independent DSMB will have interim safety reviews when: (1) approximately 25% of subjects have completed the Active Treatment Period (Visit 7), (2) approximately 50% of subjects have completed Visit 5, and (3) approximately 50% of subjects have completed the Active Treatment Period (Visit 7).

If any of the safety criteria as specified in the DSMB charter are met at these reviews, continuation of the study without alteration should be questioned as it may be an early indication of an unacceptable safety profile in the broader population. The DSMB may recommend a change to the protocol to ameliorate any safety concerns or provide recommendations regarding subsequent dosing and/or study progression/stopping as discussed in the following paragraph.

The DSMB will also be convened to review all available data if 1 or more of the study level stopping rules is met (Section 3.6.2). If any of the criteria listed below are met, the DSMB will be notified in an expedited fashion and will convene in a timely manner to review all available study data and to provide recommendations regarding subsequent dosing and/or

study progression/stopping. A decision to pause enrolment until the DSMB has reviewed the data and reached a final recommendation will be made using best clinical judgment by the DSMB chairman. Any modification recommended by the DSMB in regards to the conduct of the study will be implemented as an amendment to the protocol. In addition, the DSMB may decide to meet and review all available safety data based on other safety signals not described below. The stopping rule triggers for DSMB decision are:

- After 2 subjects experience a treatment-emergent SAE of AKI and after each subsequent subject experiences such an event.
- After 2 subjects experience an increase in serum creatinine ≥ 3 x the baseline value or a serum creatinine of ≥ 4.0 mg/dL (353.6 µmol/L) and after each subsequent subject experiences such an event.
- After 1 subject experiences a treatment-emergent SAE of acute hepatic injury and after each subsequent subject experiences such an event.
- After 1 subject experiences a treatment-emergent elevation in ALT > 3 x ULN with a concomitant elevation in total bilirubin > 2 x ULN and after each subsequent subject experiences such an event.
- After 2 subjects experience a treatment-emergent SAE of drug hypersensitivity reaction and after each subsequent subject experiences such an event.

All of the above criteria will be reported by the Investigator as SAEs in order to ensure expedited reporting of these events to the Sponsor and the DSMB as per Section 9.5.1.

3.6.2 Study-level Stopping Rules

The DSMB could recommend stopping the study based on:

- ≥ 2 subjects experience a treatment-emergent SAE of AKI

- ≥ 2 subjects experience an increase in serum creatinine to ≥ 3 x the baseline value or a serum creatinine of ≥ 4.0 mg/dL (353.6 µmol/L)
- ≥ 1 subjects experience a treatment-emergent SAE of acute hepatic injury
- ≥ 1 subjects experience a treatment-emergent elevation in ALT > 3 x ULN with a concomitant elevation in total bilirubin > 2 x ULN (ie, criteria for Hy's Law are fulfilled)
- ≥ 2 subjects experience a treatment-emergent SAE of drug hypersensitivity reaction

In addition, individual subject level criteria for discontinuation of investigational product are detailed in Section 7.1.

3.6.3 Steering Committee

A Steering Committee will provide clinical guidance on study implementation, conduct, and interpretation of results. The Steering Committee will comprise designated representatives from among the Principal Investigators, other recognized thought leaders in the field of ACS AKI, and lipidology, as well as sponsor representatives. The Steering Committee will be described in further detail in its charter.

3.6.4 Clinical Events Committee

The independent program level Clinical Events Committee (CEC) will review and adjudicate in a blinded fashion the occurrence of renal SAEs and bleeding events. 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.

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 sections below. Subject eligibility should be reviewed and documented by

the Investigator or an appropriately medically qualified member of the Investigator's study team before subjects are included in the study.

4.1.1 Inclusion Criteria

Subjects may be enrolled in the study if all of the following inclusion criteria are met:

1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements.
2. Males or females aged at least 18 years at the time of providing written informed consent.
3. Evidence of moderate RI (eGFR ≥ 30 and < 60 mL/min/1.73 m^2) before randomization, as calculated by the interactive response technology (IRT) using the CKD-EPI equation (Levey et al., 2009; Stevens et al., 2010). **The local laboratory serum creatinine value obtained at Visit 2 (Study Day 1) should be used for this calculation.**
   NOTE: The eGFR calculator on the National Kidney Foundation's website can be used for pre-screening purposes (http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm) and the equation can be found in Appendix I.
4. Evidence of myocardial necrosis in a clinical setting consistent with a type I (spontaneous) AMI 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 ischemia
      ii. New (or presumably new) significant ST/T wave changes or left bundle-branch block (LBBB)
      iii. Development of pathological Q waves on ECG
      iv. Imaging evidence of new loss of viable myocardium or regional wall motion abnormality

v. Identification of intracoronary thrombus by angiography

5. Documented evidence of stable renal function and no clinical suspicion of AKI at least 12 hours after FMC for the index AMI. For subjects undergoing angiography with or without PCI, stable renal function must be confirmed at least 12 hours after IV contrast and is defined as a serum creatinine value that is < 0.3 mg/dL increased from the pre-contrast administration value. If the local laboratory post-contrast serum creatinine value is increased ≥ 0.3 mg/dL from the pre-contrast administration value, the laboratory test may be repeated once at least 24 hours after the initial assessment to assess stable renal function. The repeat serum creatinine value must be increased < 0.3 mg/dL from the pre-contrast administration value and there must be no suspicion of AKI for the subject to be eligible to receive the first infusion (Table 7).

   NOTE: If multiple local laboratory tests are obtained before the administration of contrast agent, the serum creatinine value closest in time but before contrast administration should be used as the reference value used to assess stability of renal function.

6. Female subjects must be post-menopausal or with a negative urine pregnancy test at the screening visit and before randomization.
   a. Menopause is defined as being over the age of 60 years, or an age 45 to 60 years (inclusive) with amenorrhea for at least 1 year and a confirmatory follicle stimulating hormone (FSH) level > 30 IU/L.
   b. Women from the ages 45 to 60 years (inclusive) who are not amenorrheic for at least 1 year or who have a screening FSH ≤ 30 IU/L must use an acceptable method of contraception during the study as described below.
   c. Females of childbearing potential must be willing and able to cease breastfeeding, and use an acceptable method of contraception to avoid pregnancy during the study and for 3 months after receipt of the last dose of investigational product.
7. **NOTE**: Acceptable methods of contraception are: (1) 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, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable definitions of abstinence; (2) hormonal method; (3) 2 barrier methods, where 1 method is the male condom; or (4) use of intrauterine device (placed more than 3 months before randomization); or (5) surgical sterilization (more than 3 months before randomization). Acceptable hormonal methods include: oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen/progestin vaginal ring, or contraceptive medication implant. Acceptable barrier methods include: female or male condoms, with spermicidal foam or spermicidal jelly, or diaphragm, with spermicidal foam or spermicidal jelly. Female condom and male condom should not be used together.

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

4.1.2 Exclusion Criteria

Subjects are excluded from participating in this study if 1 or more of the following exclusion criteria are met:

1. Symptoms, biomarker elevation or ECG changes other than those of the index event that are consistent with a diagnosis of AMI but are likely not due to primary myocardial ischemia (eg, PCI or coronary artery bypass graft [CABG]-related MI, stent thrombosis, arrhythmia, heart failure, trauma, renal insufficiency, etc.) (See Third Universal Definition of MI in Appendix II)
2. Ongoing hemodynamic instability defined as any of the following:
   a. A history of New York Heart Association (NYHA) Class III or IV Heart Failure within the last year
   b. Killip Class III or IV (Appendix III)
   c. Sustained and/or symptomatic hypotension (systolic blood pressure < 90 mm Hg)

d. Left ventricular ejection fraction (LVEF) < 30%

3. Planned CABG during the Active Treatment Period
4. 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 active infectious/inflammatory hepatitis
      Note: If subject has a past 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 and/or polymerase chain reaction [PCR] negative).
   c. ALT > 3 x ULN or total bilirubin > 1.5 x ULN at time of randomization. However, subjects with a known or suspected history of Gilbert's syndrome may be eligible for study participation. The medical monitor must be contacted before enrolment of the subject to confirm eligibility (see Section 8.2.2.1, Table 7).
5. History of AKI after previous exposure to an IV contrast agent. Subjects with a history of allergy to IV contrast agent may participate in the study if they have no evidence of serious clinical sequelae at the time of consent. The medical monitor should be contacted to discuss eligibility.
6. History of current nephrotic range proteinuria defined as > 3500 mg/24 hours or > 3000 mg/g creatinine, or 4+ proteinuria on urine dipstick at screening, despite the use of angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker therapy.
7. Body weight < 50 kg
8. Known history of allergies, hypersensitivity or deficiencies as follows:
   a. Allergy to soybean or peanuts
   b. Known or suspected hypersensitivity to the investigational product, or to any excipients of the investigational product
   c. A known history of IgA deficiency or antibodies to IgA
9. 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
b. Women who are pregnant or breastfeeding
c. Participated in another interventional clinical study or had extensive blood sampling (≥ 500 mL) within 3 months. Includes administration of any other investigational agents within 3 months before the first administration of current investigational product or at any time during the study
d. 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) may be permissible. The medical monitor should be contacted to discuss eligibility.
f. Previously randomized or participating 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, and/or unwilling to allow review of medical records through end of follow-up

4.1.3 Infusion Delay and Stopping Rules

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 the first infusion of investigational product. Eligibility for the first infusion of investigational product will be determined based on local laboratory values obtained at screening according to the criteria presented in Section 8.2.1.2 and Section 8.2.2.1, Table 7.

Ongoing eligibility for all subsequent infusions of investigational product must be confirmed based on local laboratory values before each infusion according to the continuing infusion eligibility criteria presented in Section 8.2.2.2, Table 8.

Each infusion should be completed as close to the protocol-specified visit schedule as possible, ie, no fewer than 7 days and no more than 10 days between each infusion, with all 4 infusions administered within 30 days from Study Day 1 (Visit 2). An infusion may be skipped or delayed at the discretion of the Investigator if more time is necessary to confirm renal function stability or to evaluate and treat an AE before the next infusion (Section 8.2.2.2). If an infusion is skipped or delayed for a medical or safety reason, the medical monitor should be contacted, and the remaining infusions should be completed as close to the protocol-specified visit schedule as possible.

4.1.4 Study and Subject Completion, Study Treatment Discontinuation and Withdrawal from Study

4.1.4.1 Study Completion

The study will be considered completed when either the pre-specified study completion is reached (all randomized subjects either complete Visit 8/Study Day 60, have withdrawn from the study, or have been lost to follow-up) or the study is terminated early based on recommendation of the independent DSMB and endorsement by the Steering Committee.

Subjects for whom infusions of investigational product have been discontinued early should complete early termination procedures (Visit 7) and should be encouraged, if consent is not withdrawn, to continue follow-up for safety as specified through Visit 8 (Schedule of Assessments).

4.1.4.2 Subject Completion

A subject will be considered as having completed the study if he or she has completed Visit 8.

Until the study completes, all subjects who are randomized will have follow-up visits as specified by protocol (Schedule of Assessments).

If a subject is unwilling or unable to return for scheduled on-site follow-up visits, sites should attempt to collect as much visit information as possible, through telephone contact, registered mail contact, contact through family or friends, or use of publically available information. This latter source may be the only available option for subjects who withdraw consent during the study (see Section 4.1.4.4). All efforts should be made to confirm vital status at a minimum.

4.1.4.3 Study Treatment Discontinuation

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 CSL Behring LLC (CSLB) for safety, behavioral or administrative reasons (eg, due to an AE, protocol deviation, or study termination). The reason for early discontinuation of investigational product should be documented in the electronic case report form (eCRF).

In accordance with International Conference on 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 prematurely discontinues study treatment and if consent is not withdrawn, every effort should be made to inform the subject of the importance of continuing in the study to ensure that the relevant follow-up safety assessments of Visit 7 (7 to 10 days after last infusion) and Visit 8 (at least 25 days after last infusion) are performed (Schedule of Assessments). If only 1 additional study visit is to be performed after subject discontinuation, the procedures in study Visit7 should be performed. At minimum, all efforts should be made

to confirm vital status if a subject is unwilling or unable to return for scheduled on-site visits or refuses to be contacted by telephone.

In addition to the above considerations, serum creatinine, total bilirubin, and ALT must be assessed during the Active Treatment Period by the local laboratory and reviewed by the Investigator before administration of investigational product infusions 2, 3, and 4 to determine continuing eligibility; see criteria presented in Section 8.2.2.2, Table 8.

In the event that a subject experiences a hypersensitivity reaction during the infusion of investigational product, the infusion must be immediately discontinued and the subject must receive immediate medical assessment and indicated supportive management per the institutional standard of care (see Section 7.1).

If a female subject becomes pregnant, she must discontinue treatment with the investigational product, but will continue other study procedures unless not advised to do so at the discretion of the Investigator. All pregnancies must be reported according to Section 9.7.2.

4.1.4.4 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 investigational site personnel to determine the health status of the subject.

When a subject is contemplating withdrawal from the study, the Investigator (not coordinator) must discuss with the subject the importance of further follow-up and how follow-up information can be obtained (in-person visit, phone, mail, via 3rd party, review of medical records). The above discussion must be documented in the subject's medical record. If at all possible, in-person visits for subjects contemplating early withdrawal should include an early termination visit including procedures specified at Visit 7 (Schedule of Assessments). If no further follow-up is allowed due to subject's decision, the reason must be documented in the eCRF. In such instances, the site should collect vital status at a minimum

in all randomized subjects using publicly available records as permitted by national and/or local regulatory requirements.

In accordance with ICH principles of GCP, the Investigator always has the option to advise a subject to withdraw from the study. Concern for the interests of the subject must always prevail over the interests of the study.

If a subject withdraws from the study, they will continue to have access to medical care as per routine local medical practice.

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.

4.1.5 Procedures for Handling Withdrawals

Procedures for subjects who decide to withdrawal early from the study or who are withdrawn by the Investigator are discussed in Section 4.1.4.

If a subject declines further participation or is withdrawn from the study, attempts will be made to complete and document the final assessment. If at all possible, this final assessment should include the assessments and procedures specified for Visit 7 (Schedule of Assessments). If the subject withdraws from the study, and also withdraws consent for disclosure of future information, CSLB may retain and continue to use any data collected before such withdrawal of consent.

In the event that a subject withdraws from the study, the Investigator should record the reason and date of withdrawal in the eCRF and in the subject's medical records.

4.1.6 Replacement Policy

Subjects withdrawn from the study or from continued investigational product administration will not be replaced. Subject identification (ID) numbers and randomization numbers will not be reused for another subject under any circumstances, including erroneous randomization.

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 guidelines and local regulatory requirements.

CSL112 will be provided to the site as a sterile, slightly yellow, lyophilized, friable mass 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 (WFI), yielding CCI [redacted] of product ready-for-use. For the 6 g CSL112 dose to be used in this study, 3 bottles will be reconstituted for a CCI [redacted] of product.

Table 1. Key Components of CSL112

CCI [redacted]

Further details regarding preparation of CSL112 are specified in the study reference manuals.

5.1.2 Comparator Product

The comparator product will be placebo: 0.9% weight/volume (w / v) sodium chloride solution (ie, NaCl; normal saline) for IV infusion. The volume of placebo administered will be matched to the volume of CSL112 administered, ie, CCI. Placebo will be provided to the site as a registered, sterile, nonpyrogenic, colorless solution. Further details regarding the preparation of the placebo are specified in the study reference manuals.

5.2 PACKAGING, LABELING, SUPPLY AND STORAGE

5.2.1 Packaging and Labeling

CSL112 will be packaged and labeled according to current ICH Good Manufacturing Practice and GCP guidelines, and national legal requirements.

Commercially-available, sterile, WFI bottles will be sourced and labeled by CSLB or its delegate. Labeled WFI will be supplied to the study sites to use for the reconstitution of CSL112.

Commercially-available, 0.9% normal saline will be sourced and labeled specifically as "placebo" by CSLB or delegates.

5.2.2 Supply and Storage

CSL112 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.

CSL112 **MUST NOT BE FROZEN**, as this may disrupt its protein structure.

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

Further details regarding storage of CSL112 and placebo are specified in the study reference manuals.

5.3 ACCOUNTABILITY AND DESTRUCTION

All supplies of investigational product must be accounted for throughout the study. At the end of the study, the Drug Inventory Report, dated and signed by the Investigator or delegate (eg, pharmacist), must be retained at the study site as verification of final accountability of CSL112. An unblinded Clinical Monitor will conduct study drug accountability.

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 study reference manuals.

5.4 OTHER INTERVENTION(S)

Not applicable.

5.5 RESCUE THERAPY

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 via an IRT system a study-level unique subject ID number. The subject ID number will be used to identify the subject for the duration of the study. Subject ID numbers will not be reassigned or reused.

6.1.2 Randomization Procedures

Eligible subjects will be randomized in a 2:1 ratio to receive active treatment versus placebo by means of the IRT. Randomization will be stratified by eGFR (30 to < 45 mL/min/1.73 m^2 or 45 to < 60 mL/min/1.73 m^2) as calculated by the IRT using the CKD-EPI equation (Levey et al, 2009; Stevens et al, 2010) and by medical history of diabetes requiring current treatment with any anti-diabetic medication (yes or no). The IRT will assign the appropriate study treatment to each subject. CSLB or a delegate will supply the Investigator with a user guide for the IRT system. The IRT will use centralized randomization and fixed-size blocks. To ensure the study blind is maintained, a CSLB statistician / delegate not directly involved in the analysis of study results will prepare the study randomization code. The unblinded CSLB statistician/delegate will keep the randomization code on file.

6.1.3 Blinding Procedures

6.1.3.1 Blinding Method

Physical measures of blinding will be used to mask the identity of the investigational product due to the physical characteristics of CSL112 when reconstituted (ie, pale yellow/straw color with slight foaming characteristics). Information on the physical measures of blinding used to mask the identity of the investigational product will be provided in the study reference manuals.

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).

Unblinded study site personnel delegated by the Investigator will prepare the investigational product, and the IV administration 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 will not be involved in conducting or recording of any study assessment procedures.

Study site personnel delegated by the Investigator will administer the investigational product by IV infusion in a suitable peripheral or central vein. The unblinded study site personnel should be available to troubleshoot issues with the infusion pump or physical measures of blinding materials, if needed. Unblinded study site personnel may assist in the administration of the investigational product (eg, turn on the pump) in the event that a problem occurs with the infusion pump, infusion tubing, or if there is a concern that blinded site personnel may disturb the physical measures of blinding.

An unblinded Clinical Monitor will conduct study drug accountability.

Adequate procedures will be in place to ensure the integrity of the blinded data within CSLB and the study sites. CCI [redacted]. **The Investigator should not obtain a lipid panel test during the Active Treatment Period as the results may unmask treatment assignment.**

Designated sponsor representative(s) may be unblinded to specific data (ie, PK CCI [redacted] data) during the study. These individuals will not be part of the clinical study team. The translational medicine scientist and pharmacokineticist/pharmacometrician responsible for the sample analysis and PK CCI evaluation will be unblinded. However, they will agree not to

disclose the randomization code. Any preliminary PK CCI data made available during the course of the study will refer to mean data by treatment group, with descriptive statistics, without revealing any individual randomization numbers or subject numbers.

Adequate procedures will also be in place to ensure the integrity of the blinded data within the Steering Committee and CEC. These will be outlined in their respective committee charters.

Safety, PK, and other study data as requested will be provided to the DSMB as unblinded data. These procedures are outlined in the DSMB charter.

6.1.3.2 Breaking the Blind for an Emergency

The randomization code for all or 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/delegate should use IRT to identify the treatment allocation for a subject. 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.

6.1.3.3 Planned Unblinding Procedures

The randomization code will be provided to the unblinded DSMB statistician by the unblinded statistician/delegate as required. At the end of the study, the study statistician will request that the study be unblinded after authorizing database lock. The randomization codes will then be provided to the study statistician/delegate.

CSL Global Clinical Safety & Pharmacovigilance personnel may unblind the randomization code to facilitate assessment of suspected unexpected serious adverse reactions (SUSARs) experienced by any subject for expedited reporting to regulatory authorities.

6.2 DOSING AND ADMINISTRATION

The Investigator (or a medically qualified delegate) will administer or dispense the investigational product only to subjects included in this study following the procedures set out in this study protocol (Table 2). The infusions of investigational product may be administered in the hospital or the outpatient setting.

Table 2. Investigational Product Dosing Characteristics

Administration parameter	CSL112	Placebo
Route	Intravenous	Intravenous
Anatomical location	Vein (peripheral or central)	Vein (peripheral or central)
Total infusion volume		
Dose	6 g per [redacted] CC[A]	[redacted] CC[a]
Infusion duration	2 h[b]	2 h[b]

g=grams; h=hour; mL=milliliter.
[a.] Maximum anticipated dose and/or volume.
[b.] With interruptions, not to exceed 3 h.

Before infusions, laboratory assessments are required. Eligibility for the first infusion of investigational product will be confirmed based on local laboratory values obtained at screening according to the criteria presented in Section 8.2.2.1 and Table 7. 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 the first administration of investigational product. Ongoing eligibility for all subsequent infusions of investigational product on Study Days 8, 15, and 22 must be confirmed by qualified study site personnel before dose administration (ie, within 48 hours of the next infusion) according to the continuing infusion eligibility criteria presented in Section 8.2.2.2, Table 8.

Unblinded study site personnel delegated by the Investigator will prepare the investigational product, and the IV administration bag and infusion set for administration. The unblinded study site personnel will also ensure the contents remain blinded to the subject. Administration of the investigational product should be completed within 6 hours of

preparation of the solution. Blinded study site personnel (or unblinded study site personnel as per Section 6.1.3.1) delegated by the Investigator will administer the investigational product by IV infusion, in a suitable peripheral or central vein. 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. After the completion of the infusion the IV line should be flushed with saline. If the infusion is interrupted for any reason, the total duration of the infusion should not exceed 3 hours. Subjects randomized to the placebo group will receive a volume of placebo matched to the corresponding CSL112 infusion volume.

Before starting an infusion of investigational product, the Investigator or a medically qualified delegate should assess each subject for presence of hypovolemia, which may include signs of dry mouth, skin tenting, orthostasis, dizziness, etc. If hypovolemia is suspected or confirmed, the Investigator or medically qualified delegate should administer IV replacement fluid as clinically indicated. During the infusion, subjects should be encouraged to drink fluids.

Subjects should be advised to sit down or lie in a semi-supine position while receiving the infusion. If necessary, upon completion of the infusion subjects should be escorted as per site's standard of procedures to ensure their safety.

All subjects should be monitored for drug hypersensitivity reaction for at least 1 hour after the end of the first and second infusions of investigational product. Extension of the duration of the monitoring time and/or monitoring after administration of the third and fourth infusions of investigational product may be done at the discretion of the Investigator as clinically indicated. 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 7.1).

Before departing from the clinic and after completion of the infusion and all other study assessments, all subjects should be asked to void. If a subject is unable to void before leaving

the clinic, he/she should be contacted at home to determine whether or not they have been able to void.

6.3 TREATMENT COMPLIANCE

All doses of investigational product will be administered by IV infusion at the study site. Subjects will be considered to have received a complete dose of investigational product if they receive at least 80% of investigational product and cumulative infusion interruptions (if any) are for no more than a total of 60 minutes.

7. CONTRAINDICATIONS, PERMITTED THERAPIES AND PROHIBITTED 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 Development Core Safety Information document (appended to the CSL112 IB). 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 isolated 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).

In the event that a subject experiences a hypersensitivity reaction during the infusion, the infusion must be immediately discontinued and the subject must receive immediate medical assessment and indicated supportive management per the institutional standard of care.

Additional assessments are to be performed if subjects experience hypersensitivity reactions while on the study. In the event of a potential drug hypersensitivity reaction, additional assessments should be performed and follow-up is required until resolution (Section 8.2.3.6).

If a subject experiences a Grade 3 or 4 Common Terminology Criteria for Adverse Events (CTCAE) AE within 72 hours of administration of a dose of investigational product that is assessed as related to the investigational product by the Investigator, additional doses of investigational product should not be administered.

Because CSL112 is made from human blood, it may carry a risk of transmitting infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease agent). 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 virus inactivation/removal steps in the manufacturing process.

7.2 PERMITTED THERAPIES

Concomitant treatment is permitted throughout the study.

All drugs and/or procedures currently being administered to a subject at the time of signing informed consent, and which are taken in addition to the investigational product at any time during the study, are regarded as concomitant therapies and must be documented as such in the eCRF.

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) 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) may be 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 receive any prohibited therapy. If administration of any prohibited therapy becomes necessary during the study for medical reasons, the subject may be withdrawn from further study participation.

7.4 DIETARY AND LIFESTYLE RESTRICTIONS

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

7.5 OVERDOSE

Overdose is defined as any single dose 50% above the maximum dose allowed by protocol or an infusion rate that exceeds 3 mg/kg/min of sucrose. The effects of any potential overdose with CSL112 have not been studied. Refer to Section 9.7.1 for the definition of an overdose and requirements for documentation.

8. STUDY PROCEDURES, ASSESSMENTS AND VISIT SCHEDULE

8.1 CLINICAL PROCEDURES

The clinical procedures that will be conducted during this study to assess population demographics and baseline characteristics, safety, PK CCI are outlined in Table 3, Table 4, Table 5, and Table 6, respectively. The inclusion and timing of clinical procedures for this study are noted in the Schedule of Assessments. Refer to the study reference manuals for detailed instructions on how the assessments should be performed.

8.1.1 Demographics and Baseline Characteristics

Clinical procedures to be conducted to collect demographic information and baseline characteristics are provided in Table 3. These assessments will be performed at time points as detailed in the Schedule of Assessments.

Table 3. Clinical Procedures: Demographics and Baseline Characteristics

Assessment	Description
Demographics	Date of birth, years of age, sex, race, and ethnicity
Height **Weight**	Height will be recorded in centimeters (cm) Body weight will be recorded in kilograms (kg)
Medical history	Relevant medical history, including cause of CKD if known[a] Gilbert's syndrome - historical documentation (record in eCRF)
Prior/Concomitant Therapies	Prior Therapy: All medications taken by subjects in the 4 weeks before screening will be recorded, including those administered for the index AMI. Concomitant Therapy: All medications currently being administered to a subject at the time informed consent is signed and which continue to be taken in addition to investigational product during the study will be recorded.
Standard of Care Laboratory Sample: Serum Creatinine	Local laboratory tests obtained as part of standard of care may include serum creatinine measurements that will be used to determine stability of renal function after the index event or, for subjects undergoing angiography, after administration of intravenous contrast agent. If multiple laboratory tests are obtained before the administration of contrast agent, the serum creatinine value closest in time but before contrast administration should be used as the reference value to assess stability of renal function (Table 7). Results of the **local laboratory** serum creatinine tests used as the reference value to assess renal function stability should be recorded in the eCRF.
eGFR	The local laboratory serum creatinine value used to confirm stability of renal function before the first infusion of investigational product will be used to calculate baseline eGFR that will be used for stratification of randomization by eGFR. The CKD-EPI equation (see Appendix I) will be used for calculation of eGFR. This method for creatinine measurement should be traceable to IDMS standards.

AMI = acute myocardial infarction; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; IDMS = isotope dilution mass spectrometry; MI = myocardial infarction; PRBCs = packed red blood cells

[a] Including but not limited to prior MI, history of stable or unstable angina, coronary revascularization or surgery, hypertension, dyslipidemia, diabetes, congestive heart failure, peripheral arterial disease, valvular heart disease, heart rhythm disorders, cerebrovascular disease, any clinically-significant bleeding event

requiring transfusion of at least 2 units PRBCs or a discontinuation of antiplatelet or anticoagulation therapy. Also include any **relevant renal history**, particularly CKD and its cause if known, and historical renal function measures. CKD is defined as abnormalities of kidney structure or function, present for greater than 3 months, with implications for health.

8.1.2 Safety

The incidence, severity or intensity, and causality of AEs will be evaluated according to the criteria and for the duration of the observation period as specified in Section 9.

Clinical procedures to be conducted before and throughout the study to evaluate safety are provided in Table 4. Assessments for safety evaluation will be performed at time points 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. Safety assessment parameters should be repeated if the specimen is hemolyzed. Refer to the study reference manuals for detailed instructions on how the assessments should be performed.

Table 4. Clinical Procedures: Safety Assessments

Assessment	Description
Pregnancy test	Urine test for beta-human chorionic gonadotropin. Only females of child bearing potential are to be tested.
FSH measurement	FSH measurement in serum to be assessed only in amenorrheic females from the ages of 45 through 60 years, to confirm post-menopausal status.

Assessment	Description
Physical examination	As per the site's standard procedure to include examination of the skin, extremities, head, eyes, ears, nose, and throat, and the following systems: respiratory, CV, GI, musculoskeletal, neurological, lymphatic, and an assessment of general appearance. Any abnormal findings considered by the Investigator as clinically significant at the time of screening will be documented as Medical History. Any clinically significant changes occurring between screening and the end of the study will be documented in the eCRF as an AE. Physical examinations must be performed by the Investigator or a medically qualified delegate. Physical examination – should also include drug hypersensitivity findings, if relevant (Section 8.2.3.6)
12-lead ECG	Taken after the subject has rested in a supine position for ≥ 5 minutes. Heart rate, RR interval, PQ/PR duration, QRS duration, uncorrected QT duration, and the Investigator's overall interpretation will be recorded. When ECGs are scheduled to be performed at the same time as vital signs, PK CCI [redacted], the ECG should be done before these other assessments, if possible.
Vital signs	Blood pressure (systolic and diastolic) after the subject has rested in a sitting or supine position ≥ 5 minutes. Pulse rate (per minute) will be counted manually over ≥ 15 seconds and adjusted per minute or measured with an automatic blood pressure monitor. Body temperature will be recorded in degrees Celsius. Measurement can be made using either oral or tympanic methods, but the method should be consistent throughout the study for a given subject.
AE monitoring	All AEs will be monitored and recorded as described in Section 9. Reporting of bleeding events and renal SAEs includes completion of the Bleeding Event eCRF page or the Renal SAE eCRF page, respectively, with supporting documentation (hospital records and tests).
Bleeding event monitoring	Bleeding events detected by the Investigator or medically-qualified delegate will be assessed and defined using the BARC definition for bleeding (Mehran et al, 2011) (Appendix IV). Assessment includes completion of the Bleeding Event eCRF page and supporting documentation (hospital records and tests). Any bleeding event should be reported as AE (see Section 9.1).

Assessment	Description
Hypovolemia assessment	Before starting an infusion of investigational product, the Investigator or a medically qualified delegate should assess each subject for presence of hypovolemia, which may include signs of dry mouth, skin tenting, orthostasis, dizziness, etc. If hypovolemia is suspected or confirmed, the Investigator or a medically qualified delegate should administer IV replacement fluid as clinically indicated. During the infusion, subjects should be encouraged to drink fluids. Before departing from the clinic and after completion of the infusion and all other study assessments, all subjects should be asked to void. If a subject is unable to void before leaving the clinic, he/she should be contacted at home to determine whether or not they have been able to void.
Infusion Site Assessment	An assessment of the investigational product infusion site should be performed by the Investigator or a medically qualified delegate with each infusion. Any abnormal finding at the infusion site, including bruising, redness and/or swelling, should be recorded as an AE. Bruising should be assessed using the BARC criteria (Appendix IV).
Drug hypersensitivity monitoring	If a drug hypersensitivity reaction is suspected, blood samples should be obtained and sent to the central laboratory for: • quantitative immunoglobulins (IgG, IgA, IgM, IgE) • If IgA is low or not detectable, then anti-IgA antibodies will be assayed • complete blood count with differential Any drug hypersensitivity reaction should be recorded as an AE.

Assessment	Description
Hepatic injury assessment	If any subject has elevation in ALT > 3 x ULN with a concomitant elevation in total bilirubin > 2 x ULN **OR** an elevation in ALT > 5 x ULN, blood samples should be obtained and sent to the **central laboratory** within 48 to 72 hours for: • ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, GGT, amylase, and lipase • CBC with differential • CRP • PT/INR • Serology for Hepatitis A, B, C, D, E • CMV titers (IgM , IgG) • EBV titers (IgM, IgG) • Quantitative Immunoglobulins - IgG, IgM, IgE, IgA, • ANA If there is suspicion for autoimmune mediated hepatitis, blood samples should be obtained and sent to the central laboratory for: • dsDNA, anti-smooth muscle Ab, anti-mitochondrial Ab, cANCA, pANCA 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 GGT 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. Elevations in ALT > 3 x ULN with concomitant elevation in total bilirubin > 2 x ULN should be reported as a SAE as per Section 9.5.1.
Urinalysis	Urine samples will be collected and analyzed by dipstick for: • Specific gravity • pH • Blood • Glucose • Protein • Leukocyte esterase • Ketones • Bilirubin • Nitrites

Assessment	Description
	At screening only, urinalysis will be locally performed by urine dipstick. If dipstick demonstrates high grade proteinuria defined as ≥ 3+ (ie, ≥ 300 mg/dL), a urine sample should be sent to the central laboratory for urinalysis with microscopy. **For all other visits**, a urine sample will be sent to the central laboratory for urinalysis with microscopy including: • Casts • Crystals • Erythrocytes • Renal tubular epithelial cells • WBCs • Bacteria An additional sample of urine will be collected and stored for possible future biomarker analysis.
CCI [redacted]	CCI [redacted]
Hematology	Blood samples will be collected for analysis by the central laboratory: • Hemoglobin • Hematocrit • RBC count and indices • WBC counts, total and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) • Platelet count
Hemolysis	If a post-infusion hemoglobin value is ≥ 2 g/dL below the baseline value (ie, before first infusion) and is not explained by overt blood loss, assessment for hemolysis should be performed by the central laboratory: • Repeat hemoglobin level • Total and direct bilirubin, including calculation of indirect bilirubin • Serum haptoglobin level • LDH • Urine hemosiderin
Serum Biochemistry	Blood samples will be collected for analysis by the central laboratory: • Alkaline phosphatase • ALT • AST • Total bilirubin • Direct bilirubin • Albumin

Assessment	Description
	• Total Protein • Creatinine • eGFR (calculated) • BUN • Uric acid • Glucose • Calcium • Chloride • Sodium • Potassium • Bicarbonate
ALT, total bilirubin, creatinine	Blood samples will be collected for **local laboratory** analysis for assessment of subject eligibility and safety for administration of investigational product.
CCI [redacted]	CCI [redacted]
Virology blood sampling	Blood samples will be collected and stored for 1 year after completion of the clinical study report for possible future analysis for unspecified viral agents. Analysis will only be done if additional informed consent is obtained from the study subject.
Immunogenicity testing	Serum will be analyzed for the presence of binding antibodies specific to CSL112 and apoA-I.

Ab = antibody; AE = adverse event; ALT = alanine aminotransferase; ANA = anti-nuclear antibodies; apoA-I = apolipoprotein A-I; AST = aspartate aminotransferase; BARC = Bleeding Academic Research Consortium; BUN = blood urea nitrogen; cANCA = cytoplasmic anti-neutrophil cytoplasmic antibodies; CBC = complete blood count; CMV = cytomegalovirus; CRP = C-reactive protein; CV = cardiovascular; dsDNA = double stranded deoxyribonucleic acid; EBV = Epstein Barr virus; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; GGT = Gamma glutamyl transferase; GI = gastrointestinal; Ig (A, G, E, M) = immunoglobulin subtypes A, G, E, and M; INR = international normalized ratio; IV = intravenous; LDH = lactate dehydrogenase; pANCA = perinuclear anti-neutrophil cytoplasmic antibodies; CCI [redacted]; PK = pharmacokinetic; PT = prothrombin; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell

8.1.3 Pharmacokinetics CCI [redacted]

Clinical procedures to be conducted to collect samples for PK CCI [redacted] analysis are provided in Table 5 and Table 6, respectively. Refer to the timing and frequency of all clinical procedures as described in the Schedule of Assessments. Refer to the study reference manuals for details about the collection, storage, handling and transportation of biological specimens.

Table 5. Clinical Procedures: Pharmacokinetic Assessments

Assessment	Description
apoA-I, PC concentrations	Blood samples will be collected for assessment of plasma apoA-I and PC concentrations. Samples will be stored for future PK assessments if needed, ie, cholate.

apoA-I = apolipoprotein A-I, PC = phosphatidylcholine; PK = pharmacokinetic

Table 6. CCI

CCI

8.2 METHODS OF ASSESSMENT

8.2.1 Demographic and Baseline Characteristics

All demographic and baseline characteristic variables to be assessed are presented and described in Table 3.

8.2.1.1 Medical History and Assessment for Study Eligibility

The subjects' past medical history and demographic information will be documented at screening. As defined in the inclusion criteria, Section 4.1.1, assessment of renal function status for the presence of moderate RI based on eGFR and evidence of myocardial necrosis in a clinical setting consistent with a type I (spontaneous) AMI will be evaluated. A medical history will be obtained by the Investigator or a medically qualified delegate. Medical history includes all active conditions, and any condition diagnosed within 3 months before the screening visit. Such conditions may include but are not limited to prior MI, history of stable or unstable angina, coronary revascularization or surgery, hypertension, dyslipidemia, diabetes mellitus, congestive heart failure, peripheral arterial disease, valvular heart disease, heart rhythm disorders, cerebrovascular disease, or any clinically-significant bleeding event requiring transfusion of > 2 units packed red blood cells (PRBCs) within the past 3 months or a discontinuation of antiplatelet or anticoagulation therapy. If possible, documented evidence of CKD within the 6 months before admission for the index AMI should be obtained (eg, prior serum creatinine, eGFR, proteinuria, suspected etiology of CKD).

8.2.1.2 Screening and Randomization on Same Day

Screening and randomization of subjects may occur on the same day (Study Day 1 of the Active Treatment Period) provided that the minimum time for assessment of renal function stability is adhered to before administration of the first infusion of investigational product (Section 8.2.2.1). To receive the first infusion of investigational product, subjects must have documented evidence of stable renal function and no suspicion of AKI at least 12 hours after FMC for the index AMI event. For subjects undergoing angiography, stable renal function is defined as a local laboratory serum creatinine value at least 12 hour after contrast administration that is increased < 0.3 mg/dL from the pre-contrast administration value. See Section 8.2.2.1 for repeating post-contrast assessments of renal function. The screening period up to and including randomization must occur within 5 days of FMC for the index AMI.

Local laboratory values for serum creatinine, ALT, and total bilirubin obtained as part of standard of care may be used for evaluating renal and hepatic function. If multiple laboratory tests are obtained before the administration of contrast agent, the serum creatinine value closest in time but before IV contrast administration should be used to assess stable renal function. Similarly, the serum creatinine value obtained after, but closest in time to the minimum window required after FMC or, for subjects undergoing angiography, after IV contrast administration should be used to confirm renal function stability before administration of the first infusion (Table 7). The pre-contrast and baseline serum creatinine values used to confirm renal function stability must be documented in the eCRF.

If screening and randomization occur on the same day, all protocol specified procedures and assessments indicated at Visit 1 and Visit 2 (Baseline/before infusion) in the Schedule of Assessments must still be performed, although certain assessments do not need to be duplicated. **If Visits 1 and 2 are combined**, there may be a single blood draw for central laboratory serum biochemistry, and local laboratory ALT, total bilirubin, and serum creatinine. Both a local laboratory and central laboratory urinalysis should be performed. There may be 1 ECG. Single assessments of vital signs, concomitant medications, and AEs are also acceptable.

8.2.2 Infusion Eligibility

8.2.2.1 First Infusion

In addition to confirming hemodynamic stability, both hepatic (ALT and total bilirubin) and renal (serum creatinine) function, based on **local laboratory** values, must be reviewed by the Investigator and determined to be within acceptable limits before administration of the first infusion of investigational product (Table 7). The screening period up to and including randomization must occur within 5 days of FMC for the index AMI.

For the pre-infusion assessment of hepatic function before the first infusion, the following criteria apply:

- ALT value must be ≤ 3 x ULN and total bilirubin value must be ≤ 1.5 x ULN (Section 4.1.2).
- If the baseline ALT is > 3 x ULN, the subject **is not** eligible for dosing.
- If the baseline total bilirubin value is > 1.5 x ULN, the subject **is not** eligible for dosing **unless** there is historical documentation of Gilbert's syndrome. **In this instance, the Investigator or a medically qualified delegate should confirm historical documentation of Gilbert's syndrome with the medical monitor.**
- A repeat baseline assessment for hepatic function is **not** permitted.

All subjects must have documented evidence of stable renal function and no suspicion of AKI at least 12 hours after FMC for the index AMI. For subjects undergoing angiography with or without PCI, stable renal function is defined as a serum creatinine value at least 12 hours after contrast administration that is increased < 0.3 mg/dL from the pre-contrast administration value (Table 7).

If multiple laboratory tests are obtained before the administration of contrast agent, the serum creatinine value closest in time but before IV contrast administration should be used as the reference value to assess stable renal function. Similarly, the serum creatinine value obtained after, but closest in time to the minimum time required after FMC for the index AMI or, for subjects undergoing angiography, after IV contrast administration should be the baseline value used to confirm renal function stability before administration of the first infusion. These pre-contrast and baseline serum creatinine values used to confirm renal function stability must be documented in the eCRF.

If the post-contrast serum creatinine value is increased ≥ 0.3 mg/dL from the pre-contrast administration value, the laboratory test may be repeated once at least 24 hours later to assess stable renal function. The repeat serum creatinine value must be increased < 0.3 mg/dL from the pre-contrast administration value for the subject to be eligible, provided no clinical suspicion of AKI exists.

Table 7. Key Hepatic and Renal Laboratory Parameters and Protocol Requirements for Study/First Infusion Eligibility

Protocol Parameter	Alanine Aminotransferase (ALT; absolute level)		Total Bilirubin (absolute level)		Post-Contrast Serum Creatinine (change from pre-contrast administration value in mg/dL)[c]	
	≤3x ULN	>3x ULN	≤1.5x ULN	>1.5x ULN	<0.3 increase	≥0.3 increase
Initial assessments[a]	Eligible	**Not eligible**	Eligible	Not eligible unless Gilbert's Syndrome[b]	Eligible	Delay eligibility and infusion: Repeat once at least 24 h after initial assessment[d]
Repeat assessment	N/A		N/A		Eligible	**Not eligible**

ALT = alanine aminotransferase; AMI = acute myocardial infarction; CRF=case report form; FMC=first medical contact; h = hour; IV = intravenous; mg/dL= milligram per deciliter; N/A = not applicable; ULN = upper limit of normal

a. Laboratory assessments performed during screening (Visits 1 and 2 before infusion) must be reviewed by the Investigator before administration of investigational product. Screening and randomization may occur on the same day (Study Day 1) provided that test results are available for ALT, total bilirubin, and serum creatinine to assess hepatic function and to confirm renal function stability at least 12 hours after FMC for the index AMI event. For subjects who have received IV contrast agent, the values for serum creatinine must have been obtained before and at least 12 hours after the administration of contrast (Section 8.2.1.2). **Local laboratory values obtained as part of standard of care may be used for this purpose**.

b. Confirm historical documentation with the Medical Monitor and record in medical history CRF. If Gilbert's syndrome, use indirect bilirubin for this determination.

c. Serum creatinine 0.3 mg/dL = 26.5 µmol/L

d. The repeated value is assessed to check for any trajectory/continued rise in an effort to establish stable renal function at baseline. There must be no suspicion of AKI.

8.2.2.2 Subsequent Infusions

For infusions 2, 3, and 4, hepatic (ALT and total bilirubin) and renal (serum creatinine) function is to be assessed within 48 hours of the infusion using the **local laboratory**. The results must be reviewed by the Investigator and determined to be clinically stable before each administration of investigational product. Eligibility for continued administration of investigational product will be based on the criteria presented below and summarized in Table 8.

For assessment of hepatic function before infusion 2 or subsequent infusions, the following criteria apply:

- ALT value must be ≤ 3 x ULN and total bilirubin value must be ≤ 1.5 x ULN for eligibility
- If the ALT value is > 3 x ULN or total bilirubin value is > 1.5 x ULN, the infusion must be delayed and ALT and/ or total bilirubin values may be repeated once at least 24 hours after the initial assessment to determine dosing eligibility and hepatic stability. If the subject has a medical history of Gilbert's syndrome, indirect bilirubin may be used instead of total bilirubin to determine dosing eligibility.
- If the repeated assessment of ALT value is > 3 x ULN **OR** total bilirubin value is > 1.5 x ULN and the observed variation is not attributable to Gilbert's syndrome, the subject is not eligible for continued dosing and all remaining infusions must be discontinued. If the subject has a history of Gilbert's syndrome, indirect bilirubin may be used instead of total bilirubin to determine dosing eligibility.

For assessment of renal function before infusion 2 or subsequent infusions, the following criteria apply:

- Change from baseline (pre-infusion on Study Day 1) in serum creatinine must be < 0.3 mg/dL.

- If the serum creatinine value is increased 0.3 to 0.5 mg/dL from baseline value before infusion 2 or subsequent infusions, the subject is eligible for dosing if the observed variation may be attributable to changes in concomitant medications with hemodynamic effect or other clinical factors (eg, IV fluid discontinued) or falls within range of variability previously observed for the subject. If the variation cannot be attributed to above, then perform repeat assessments before dosing as per Table 8.
- If the serum creatinine value is increased > 0.5 mg/dL from baseline value before infusion 2 or subsequent infusions, the infusion should be delayed until a minimum of **2** subsequent serum creatinine determinations performed at least 24 hours apart are < 0.3 mg/dL increased from the baseline. If the creatinine does not return to < 0.3 mg/dL, on 2 subsequent repeat assessments, the infusion will be delayed, and a repeat serum creatinine will be assessed at 7 days (± 24 h) from the pre-infusion assessment (ie, the initial assessment before the delayed dose). At the time of the delayed infusion, the medical monitor should be contacted for further guidance regarding timing of subsequent infusions of investigational product. If after 7 days, the creatinine is < 0.3 mg/dL increased from baseline, an **additional serum creatinine** should be performed at least 24 hours later in order to confirm that the value is still < 0.3 mg/dL increased from baseline before subsequent dosing. The subject will be eligible only if ≥ 2 repeat values performed at least 24 hours apart are each < 0.3 mg/dL increased from baseline. In addition, dosing should proceed only if the subject is assessed as clinically stable by the Investigator. If after 7 days the creatinine is still ≥ 0.3 mg/dL increased from the baseline value, all subsequent infusions will be discontinued (see Table 8).

If any administration of investigational product is discontinued due to these eligibility laboratory criteria, the abnormal laboratory parameter should be followed with central laboratory testing performed at 48- to 72-hour intervals, or as clinically indicated, until the abnormal value returns to the subject's pre-infusion baseline value or renal and/or hepatic function is stabilized.

Table 8. Key Hepatic and Renal Laboratory Parameters and Protocol Requirements for Subsequent/Continuing Infusion Eligibility

Protocol Parameter	Alanine Aminotransferase (ALT; absolute level)		Total Bilirubin (absolute level)		Serum Creatinine (change from baseline value in mg/dL)		
	≤ 3x ULN	> 3x ULN	≤ 1.5x ULN	> 1.5x ULN	< 0.3[b] increase	0.3 to 0.5 increase	> 0.5 increase
Initial assessment before infusion 2, 3 or 4[a]	Eligible	Delay infusion: Repeat once at least 24 h after initial assessment	Eligible	Delay infusion: Repeat once at least 24 h after initial assessment (If Gilbert's syndrome, use indirect bilirubin for this determination.)	Eligible	Eligible if meet criteria in footnote [c]	Delay infusion: Repeat creatinine ≥ 24 h after initial assessment
Repeat assessment #1[d]	Eligible	**Discontinue infusions**: follow-up as per protocol	Eligible	**Discontinue infusions**	Perform repeat assessment #2 in ≥ 24 h to confirm	**Delay current infusion:** Repeat serum creatinine in 7 days (±24 h) to determine subsequent renal eligibility and contact medical monitor for further guidance. Eligible if ≥ 2 repeat values performed at least 24 hours apart are each < 0.3 mg/dL increased from baseline [e]	
Repeat assessment #2[d]	**N/A**				Eligible if ≥ 2 repeat values performed at least 24 hours apart are each < 0.3 mg/dL increased from baseline		

h = hour; IV = intravenous; mg/dL= milligram per deciliter; N/A = not applicable; ULN = upper limit of normal

a. Laboratory assessments are performed up to 48 hours before infusions 2, 3, and 4, and must be reviewed by the Investigator before administration of investigational product.

b. 0.3 mg/dL = 26.5 µmol/L

c. Eligible if observed variation **MAY BE** attributable to changes in concomitant medications with hemodynamic effect or other clinical factors (eg, IV fluid discontinued) or falls within range of variability previously observed for the subject. If variation cannot be attributable to above, perform repeat assessments.

d. Repeat laboratory assessments should be performed ≥ 24 hours apart to determine eligibility as clinically indicated.

e. If this criterion is met, a repeat serum creatinine assessment will be performed 7 days (±24 h) from the initial pre-infusion assessment (ie, initial assessment before the delayed dose). If after 7 days, the creatinine is < 0.3 mg/dL increased from baseline, an additional serum creatinine should be performed at least 24 hours later in order to confirm that the value is still < 0.3 mg/dL increased from baseline before subsequent dosing. The subject will be eligible only if ≥ 2 repeat values

performed at least 24 hours apart are each < 0.3 mg/dL increased from baseline. In addition, dosing should proceed only if the subject is assessed as clinically stable by the Investigator. If at the time of this subsequent (ie, second) creatinine determination, the value is still ≥ 0.3 mg/dL increased from baseline, all subsequent infusions will be discontinued.

8.2.3 Safety

8.2.3.1 Adverse Events

Incidence, grade, and causality of AEs, including SAEs, will be evaluated according to the criteria specified in Section 9. The period of observation of AEs (and SAEs) extends from the time the subject provides signed informed consent until the subject completes the study, as specified in Section 9.4. Procedures for reporting AEs, and SAEs, are specified in Section 9.5 and Section 9.6, respectively.

Reporting of bleeding events and renal SAEs includes completion of the Bleeding Event eCRF page or the Renal SAE eCRF page, respectively, with supporting documentation (hospital records and tests).

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.

Each individual manifestation of an AE should be graded individually for severity (see Section 9.2).

Details of the definitions and categorization of AEs, and procedures for the reporting of AEs, are available in Section 9.

8.2.3.2 Vital Signs

The Investigator or qualified delegate will take vital signs at screening, before the each infusion of investigational product, at the end of infusion of investigational product, and at any follow-up visits as specified in the Schedule of Assessments. Blood pressure (systolic and diastolic) and pulse rate must be measured with the subject in a supine or seated position after resting for at least 5 minutes.

Blood pressure measurements should be taken from the same arm throughout the study using an automated blood pressure monitor that uses an oscillometric method. The same arm should **not** be used for blood sample collections and blood pressure assessments, if possible. At screening, blood pressure measurements may be repeated twice. If there is a clinically significant change in blood pressure from the previous reading, measurements will be repeated immediately to confirm the change.

Body temperature can be measured either orally or tympanically, but the method should be consistent throughout the study for a given subject. Height will be measured at Visit 1 only.

8.2.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. ECG intervals (eg, RR, PQ/PR, QRS, and uncorrected QT) will be measured. Clinically significant abnormal findings as determined by the Investigator are to be recorded. After the first infusion of investigational product, any new clinically significant abnormal findings should be recorded as AEs (see Section 9.5).

8.2.3.4 Bleeding Events

Assessment of any bleeding events, including assessment of the infusion site for bruising, redness or swelling, will be performed at each visit after randomization (including baseline), up to and including Visit 8. The event should be recorded as an AE (see Section 9.5) and assessed by using the BARC criteria as outlined in Appendix IV. The Bleeding Event eCRF page should also be completed along with supporting source documents (hospital records and tests).

8.2.3.5 Physical Examination

The Investigator or a medically qualified delegate will perform a physical examination covering the following body systems (head and neck, CV, respiratory, gastrointestinal (GI), musculoskeletal, neurologic, and integumentary systems) during screening and at the end of the Active Treatment Period as specified in the Schedule of Assessments. Clinically

significant abnormal findings at screening should be recorded as medical history. After the first infusion of investigational product, new clinically significant abnormal findings should be recorded as AEs (see Section 9.5). Physical examination findings should also include drug hypersensitivity reactions if relevant (see Section 8.2.3.6).

8.2.3.6 Drug Hypersensitivity Monitoring

Drug hypersensitivity findings may include: allergic reactions, bronchospasm/wheezing, generalized rash, anaphylaxis, etc. In the event that a subject experiences a hypersensitivity reaction during the infusion, the infusion is to be stopped immediately, and additional assessments are to be performed including:

- Blood samples for quantitative immunoglobulins (IgG, IgM, IgE, and IgA) and complete blood count with differential (Section 8.1.2, Table 4). Anti-IgA antibodies will be performed if clinically indicated at the central laboratory.
- 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: rash, swelling, hives, itching, 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, etc.).

8.2.3.7 Laboratory Procedures

Details regarding laboratory procedures / assessments to be performed in this study are provided in the subsequent subsections. The local laboratory is to be used for all laboratory assessments that must be reviewed in real time, ie, values taken to determine study eligibility and dosing decisions. **All laboratory assessment samples should also be sent to the central laboratory for analysis.**

Clinical laboratory test results 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 or SAEs. If clinically significant abnormal laboratory test results are identified after investigational product infusion, the test(s) will be repeated until the abnormal values return to normal and/or baseline or stabilize (Section 8.2.2.2). Safety parameters should be repeated if the specimen is hemolyzed.

An abnormal laboratory value should be deemed clinically significant if any of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened since baseline.
- The abnormality is of a degree that requires active management (ie, change of dose), discontinuation of the study product, close observation, more frequent follow-up assessments or further diagnostic investigation.
- If the Investigator is able to provide a differential diagnosis for the abnormal clinical laboratory result, the AE is to be recorded accordingly. In the absence of an associated clinical sign or symptom, and if only a single laboratory value is deemed clinically significant, the abnormal laboratory value is to be recorded as the AE.

Any laboratory test result abnormality fulfilling the criteria for an AE or and SAE should be reported as such (see Section 9.5).

8.2.3.7.1 Serum Biochemistry

Sampling for serum biochemistry will be obtained for analysis by the central laboratory at time points listed in the Schedule of Assessments and the values will be used for **safety** analysis (Table 4).

Sampling for ALT, total bilirubin and serum creatinine should be obtained from the **local laboratory** to assess for eligibility and safety for administration of investigational product. Results must be reviewed by the Investigator before infusions on Study Days 1, 8, 15, and 22

(Section 8.2.1.2 and 8.2.2). The sample may be obtained up to 48 hours before the infusions 2, 3, and 4 on Study Days 8, 15, and 22.

If a subject is found to have an ALT elevated to > 3 x ULN with a concomitant elevation in total bilirubin to >2 x ULN OR an ALT elevated to > 5 x ULN, additional assessments should be performed within 48 to 72 hours and sent to the central laboratory for analysis as detailed in Section 8.1.2, Table 4 (Hepatic injury assessment).

8.2.3.7.2 Hematology and Hemolysis

Sampling for hematology by the central laboratory will include hemoglobin, hematocrit, platelets, red blood cell (RBC) indices and white blood cell (WBC) counts and differential as outlined in Table 4 and at time points listed in the Schedule of Assessments.

If any subject is found to have a decrease in hemoglobin ≥ 2 g/dL from the Visit 2 baseline value and/or is suspected of having hemolysis (ie, decrease is not explained by overt blood loss), the subject must have a hemolysis assessment that includes repeat assessment of hemoglobin level, serum haptoglobin levels, LDH, total and direct bilirubin levels, including the calculation of indirect bilirubin, and urine hemosiderin. Hemolysis should also be considered if total bilirubin > 2 x ULN is observed.

8.2.3.7.3 Urinalysis

Urinalysis will be performed as outlined in Table 4 and at time points listed in the Schedule of Assessments. At screening, if the locally performed dipstick is positive for high grade proteinuria defined as ≥ 3+ (ie, ≥ 300 mg/dL), a urine sample will be sent to the central laboratory for urinalysis and microscopic examination.

CCI [redacted]

CCI [redacted]

[redacted].

8.2.4 Pharmacokinetics

Blood samples will be collected at time points listed in the Schedule of Assessments for determination the PK of CSL112 through analysis of apoA-I and PC plasma concentrations (Table 5). Sample analysis will be conducted as detailed in the study reference manuals.

8.2.5 CCI

8.2.5.1 CCI

CCI

8.2.5.2 CCI

CCI

8.3 RETENTION OF SAMPLES

Samples intended for storage and/or future analyses (eg, Archival Blood Sample, Virology Sample, and Urine Sample) will be collected at time point(s) specified in the Schedule of Assessments.

- The decision to assess additional biomarkers (eg, lipid, cardiac, renal, or inflammatory) from an archival blood and/or urine sample may be made by the Steering Committee and

based on the latest available information on the utility of such measurements. This sample will be stored for up to 10 years after completion of the study, or for the duration permitted by national or local regulations, and destroyed upon notification by the Steering Committee. These analyses may be used for future planning and / or exploratory analyses. No genotypic analysis will be performed utilizing these samples.

- The virology samples are taken for possible future assessment of currently unspecified viral agents. A minimum of 2 samples will be stored for up to 1 year after the completion of the clinical study report for possible virology testing. If testing is required, a separate protocol will be written by the sponsor and Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approval for the protocol sought; upon IRB / IEC approval, impacted subjects would need to provide written informed consent before virology testing of their samples could be conducted.

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.

8.5 VISIT SCHEDULE

This study consists of screening, an Active Treatment Period and a Safety Follow-up Period with a total of 8 scheduled visits (Figure 1). The assessments to be conducted at scheduled visits within each of these study parts are outlined in the following sections. The timing and frequency of the study visits are described in the Schedule of Assessments. Time windows for assessments are detailed in Table 9.

Table 9. Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Screening)	Up to 5 days after FMC for index AMI

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 2 (Study Day 1; pre-infusion baseline and first infusion)	First infusion starts 0 to 5 days after FMC for AMI and at least 12 hours after angiography, if performed
Visit 3 (Study Day 2)	24 to 48 hours (±6 h) after start of first infusion
Visits 4 to 6 (pre-infusion assessments and infusions 2-4 on Study Days 8, 15, and 22, respectively)	Visit 4 is 7 to 10 days after Visit 2; Visits 4 to 6 are separated by 7 to 10 days
Visit 7 (Study Day 29)	7 to 10 days after Visit 6
Visit 8 (Study Day 60)	60 (+ 7) days after first infusion provided that the visit occurs no less than 25 days after the last infusion
Blood collections for PK CCI	Before infusion: up to 30 min before start of infusion End of infusion: up to 30 min after end of infusion

AMI = acute myocardial infarction; FMC=first medical contact for index event; h = hour; min = minutes; PK = pharmacokinetic; CCI

8.5.1 Screening (Visit 1, Study Day -5 to Study Day -1)

Potentially eligible subjects who are suspected of AMI will be assessed to determine if inclusion criteria are met and no exclusion criteria are present. Those who qualify will be given an opportunity to provide written 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. Specifically, a serum creatinine, obtained as standard of care assessment and before obtaining written informed consent will be recorded on the eCRF to provide a renal function reference point for comparison of the pre-angiography standard of care value to the pre-infusion (ie, baseline) study value.

Depending on time of event and time required from evaluation in the Emergency Department, cardiac catheterization laboratory, administration of contrast dye, and assessment of renal and hepatic function, screening may occur up to 5 days after FMC for the index AMI. First medical contact (FMC) is defined as the point in time (ie, clock start) at which the subject

arrives at the hospital emergency department (ie, door time) or cardiac catheterization laboratory, for evaluation and treatment of AMI.

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.
- Medical history, including active medical conditions and medical or surgical history diagnosed within 3 months before the screening visit (including but not limited to prior MI, diabetes mellitus, GI bleed, or any other clinically-significant bleeding event requiring transfusion of > 2 units PRBCs within the past 3 months). Specifically for history of CKD, evidence of CKD within the 6 months before admission for the index AMI should be obtained if possible (eg, prior serum creatinine, eGFR, proteinuria, or suspected etiology of CKD).
- Demography
- Prior / concomitant medication review
- Review of inclusion and exclusion criteria (including relevant clinical laboratory tests and method of contraception)
- Height (in cm)
- Body weight (in kg)
- 12-lead ECG
- Physical examination (includes examination of head and neck, CV, respiratory, GI, musculoskeletal, neurologic and integumentary systems; any abnormal findings should be recorded on the medical history eCRF)

- Vital signs (blood pressure [supine or seated systolic and diastolic], pulse rate [after resting for 5 minutes], and body temperature (oral or tympanic)
- AE assessment
- Urine pregnancy test
  - Required for all women of child-bearing potential.
- FSH test by central laboratory (for amenorrheic females between the ages of 45 and 60 years, to confirm post-menopausal status)
- Serum biochemistry by central laboratory
- ALT, total bilirubin, and serum creatinine **by local laboratory**. These results must be reviewed by the Investigator to determine hepatic and renal function stability for study eligibility (Section 8.2.2.1).
- Urinalysis. At screening only, urinalysis will be locally performed by urine dipstick. If dipstick demonstrates high grade proteinuria defined as ≥ 3+ (ie, ≥ 300 mg/dL), a urine sample should be sent to the central laboratory for urinalysis.
- Use IRT to assign the subject identification number

Subjects who complete all of these assessments and who fulfil the eligibility criteria (ie, eligible subjects) will be enrolled into the study.

If the subject is not eligible for the study, the primary reason for screen failure must be entered in the IRT system.

Screening and randomization of subjects may occur on the same day (Study Day 1 of Active Treatment Period) provided that the minimum time after FMC for the index AMI event or administration of IV contrast agent is adhered to for confirmation of renal function stability before administration of the first infusion of investigational product. If the first infusion of investigational product is to be administered on the same day that screening assessments were performed, the **local laboratory** test results obtained at screening may be used to assess for hepatic function testing within acceptable limits and renal function stability if the criteria outlined in Section 8.2.1.2 are met.

8.5.2 Active Treatment Period

8.5.2.1 Visit 2 (Study Day 1)

The following **baseline assessments** are to be made in the study unit **immediately before administration of the first infusion** of investigational product on Study Day 1:

- Concomitant medication review
- Confirm inclusion and exclusion criteria
- Vital signs
- 12-lead ECG
- Assessment for hypovolemia
- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Bleeding event assessment: if a bleeding event occurs, the bleeding event should be recorded as an AE and a BARC score assigned (Appendix IV); the Bleeding Event eCRF page with supporting source documentation should be completed.
- AE assessment
- Blood collection for:
  - Serum biochemistry by central laboratory

    Serum creatinine, total bilirubin and ALT **by local laboratory**. Test results must be reviewed by the Investigator to assess for hepatic function tests within acceptable limits and stable renal function before the first infusion (Section 8.2.2.1).
  - CCI [redacted]
  - Hematology by central laboratory
  - Virology sample
  - Immunogenicity testing
  - PK assessment
  - CCI [redacted]
    - CCI [redacted]
    - CCI [redacted]

  - CCI [redacted]
  - [redacted]
  - Archival blood sample for central laboratory
- Urine collection for
  - Urinalysis (including dipstick and microscopic examination by central laboratory)
  - CCI [redacted]
  - Archival urine sample (for central laboratory) for possible future renal biomarker analysis
- Use IRT to (a) calculate eGFR based on the subject's age, sex, race, and the serum creatinine value (see inclusion criterion 3, Section 4.1.1) and (b) randomize the subject if eligible

Investigational product infusion #1: 2-hour IV infusion of CSL112 or placebo

The first infusion of investigational product should occur when the subject is considered to be clinically stable by the Investigator, but no earlier than 12 hours after FMC for the index AMI or, for those undergoing angiography, no earlier than 12 hours after contrast administration. The infusion of investigational product may occur in the hospital or in the outpatient setting and must not be administered any later than 5 days after FMC for the index AMI event.

If the first infusion of investigational product is to be administered on the same day that the screening assessments are performed (Study Day 1), the minimum time for assessing renal function stability must be adhered to (Section 8.2.1.2).

Assessments at the **start of infusion (SOI)** of investigational product

- AE assessment

Assessments after the **end of infusion (EOI)** of investigational product

- Vital signs (blood pressure [supine systolic and diastolic], pulse rate, body temperature)

- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Post-infusion monitoring for drug hypersensitivity reaction for at least 1 hour after the end of investigational product infusion
- AE assessment
- Blood collection for:
  - PK assessment
  - CCI [redacted]

8.5.2.2 Visit 3 (Study Day 2 + 1 day)

The following procedures will be performed **24 to 48 hours (± 6 h) after the start of the first infusion** of investigational product:

- Concomitant medication review.
- Vital signs
- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Bleeding event assessment: if a bleeding event occurs, the bleeding event should be recorded as an AE and a BARC score assigned (Appendix IV); the Bleeding Event eCRF page with supporting source documentation should be completed.
- AE assessment
- Blood collection for:
  - Serum biochemistry by central laboratory
  - Serum creatinine, total bilirubin and ALT **by local laboratory**. Test results must be reviewed by the Investigator to assess for hepatic function tests within acceptable limits and stable renal function.
  - CCI [redacted]

– PK assessment
– CCI

- Urine collection for:
  – Urinalysis (including dipstick and microscopic examination by central laboratory)
  – CCI
  – Archival urine sample (for central laboratory) for possible future renal biomarker analysis

8.5.2.3 Visit 4 (Study Day 8 + 3 days)

The following assessments are to be made in the study unit **immediately before administration of the second infusion** of investigational product:

- Concomitant medication review
- Vital signs
- Assessment for hypovolemia
- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Bleeding event assessment: if a bleeding event occurs, the bleeding event should be recorded as an AE and a BARC score assigned (Appendix IV); the Bleeding Event eCRF page with supporting source documentation should be completed.
- AE assessment
- Blood collection for:
  – Serum biochemistry by central laboratory

  - Serum creatinine, total bilirubin and ALT **by local laboratory**. Test results must be reviewed by the Investigator to assess for stable hepatic and renal function before dosing. The sample may be obtained up to 48 hours before dosing and may be repeated at least 24 hours after the initial assessment as per Table 8.
  - CCI
  - Hematology panel by central laboratory
  - CCI

- Urine collection for:
  - Urinalysis (including dipstick and microscopic examination by central laboratory)
  - CCI
  - Archival urine sample (for central laboratory) for possible future renal biomarker analysis

Investigational product infusion #2: 2-hour IV infusion of CSL112 or placebo

Assessments at the **start of infusion (SOI)** of investigational product

- AE assessment

Assessments after the **end of infusion (EOI)** of investigational product

- Vital signs
- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Post-infusion monitoring for drug hypersensitivity reaction for at least 1 hour after the end of investigational product infusion
- AE assessment

8.5.2.4 Visit 5 (Study Day 15 +3 days)

The following assessments are to be made **immediately before administration of the third infusion** of investigational product:

- Concomitant medication review
- Vital signs
- Assessment for hypovolemia
- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Bleeding event assessment: if a bleeding event occurs, the bleeding event should be recorded as an AE and a BARC score assigned (Appendix IV); the Bleeding Event eCRF page with supporting source documentation should be completed.
- AE assessment
- Blood collection for:
  - Serum biochemistry by central laboratory
  - Serum creatinine, total bilirubin, and ALT **by local laboratory**. Test results must be reviewed by the Investigator to assess for stable hepatic and renal function before dosing. The sample may be obtained up to 48 hours before dosing and may be repeated at least 24 hours after the initial assessment as per Table 8.
  - Hematology panel by central laboratory
  - [redacted]
- Urine collection for:
  - Urinalysis (including dipstick and microscopic examination by central laboratory)
  - [redacted]
  - Archival urine sample (for central laboratory) for possible future renal biomarker analysis

Investigational product infusion #3: 2-hour IV infusion of CSL112 or placebo

Assessments at the **start of infusion (SOI)** of investigational product

- AE assessment

Assessments after the **end of infusion (EOI)** of investigational product

- Vital signs

- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Post-infusion monitoring for drug hypersensitivity reaction for at least 1 hour after the end of investigational product infusion at the discretion of the Investigator.
- AE assessment

8.5.2.5 Visit 6 (Study Day 22 +3 days)

The following assessments are to be made **immediately before administration of the fourth infusion** of investigational product:

- Concomitant medication review
- Vital signs
- Assessment for hypovolemia
- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Bleeding event assessment: if a bleeding event occurs, the bleeding event should be recorded as an AE and a BARC score assigned (Appendix IV); the Bleeding Event eCRF page with supporting source documentation should be completed.
- AE assessment
- Blood collection for:
  - Serum biochemistry by central laboratory
  - Serum creatinine, total bilirubin, and ALT **by local laboratory**. Test results must be reviewed by the Investigator to assess for stable hepatic and renal function before dosing. The sample may be obtained up to 48 hours before dosing and may be repeated at least 24 hours after the initial assessment as per Table 8.
  - CCI [redacted]
  - Hematology panel by central laboratory
  - PK assessment
  - CCI [redacted]
- Urine collection for:
  - Urinalysis (including dipstick and microscopic examination by central laboratory)

- CCI [redacted]
- Archival urine sample (for central laboratory) for possible future renal biomarker analysis

Investigational product infusion #4: 2-hour IV infusion of CSL112 or placebo

Assessments at the **start of infusion (SOI)** of investigational product

- AE assessment

Assessments after the **end of infusion (EOI)** of investigational product

- Vital signs
- Infusion site assessment (note any abnormal finding, including bruising, redness and/or swelling, as an AE)
- Post-infusion monitoring for drug hypersensitivity reaction for at least 1 hour after the end of investigational product infusion at the discretion of the Investigator
- AE assessment
- Blood collection for:
  - PK assessment
  - CCI [redacted]
    CCI [redacted]

8.5.2.6 Visit 7 (Study Day 29 +3 days)

The following procedures will be performed at the **last visit of the Active Treatment Period**:

- Concomitant medication review
- Body weight (in kg)
- 12-lead ECG
- Physical examination (includes examination of head and neck, CV, respiratory, GI, musculoskeletal, neurologic and integumentary systems)
- Vital signs

- Bleeding event assessment: if a bleeding event occurs, the bleeding event should be recorded as an AE and a BARC score assigned (Appendix IV); the Bleeding Event eCRF page with supporting source documentation should be completed.
- AE assessment
- Blood collection for:
  - Serum biochemistry by central laboratory
  - CCI [redacted]
  - Hematology by central laboratory
  - Virology sample
  - Immunogenicity testing
  - CCI [redacted]
  - Archival blood sample for central laboratory
- Urine collection for:
  - Pregnancy test. Required for all women of child-bearing potential.
  - Urinalysis (including dipstick and microscopic examination by central laboratory)
  - CCI [redacted]
  - Archival urine sample (for central laboratory) for possible future biomarker analysis

8.5.3 Safety Follow-up Period

The 30 days after Visit 7 is the Safety Follow-up Period. Visit 8 (Study Day 60 + 7 days) is the end of study. The following assessments will be made at Visit 8:

- Concomitant medication review
- Body weight (in kg)
- 12-lead ECG

- Physical examination (includes examination of head and neck, CV, respiratory, GI, musculoskeletal, neurologic and integumentary systems)
- Vital signs
- Bleeding event assessment: if a bleeding event occurs, the bleeding event should be recorded as an AE and a BARC score assigned (Appendix IV); the Bleeding Event eCRF page with supporting source documentation should be completed.
- AE assessment
- Blood collection for:
  - Serum biochemistry by central laboratory
  - Hematology by central laboratory
  - Virology sample
  - Immunogenicity Testing
  - CCI [redacted]
  - Archival blood sample for central laboratory
- Urine collection for:
  - Pregnancy test. Required for all women of child-bearing potential.

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.

The period of observation for AEs extends from the time the subject gives informed consent until the end of study (see Section 9.4 for further details).

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- 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 pre-existing 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, chemotherapy).
- Overdose of investigational product or any concomitant therapy that does not result in any adverse 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 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 pre-existing 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 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.

9.1.3 Adverse Events of Special Interest

The following AEs are of special interest for which ongoing monitoring and/or expedited reporting by the Investigator is required as per Section 9.5.1:

9.1.3.1 Stage 3 Acute Kidney Injury

Acute kidney injury for this purpose will be defined as an elevation in serum creatinine during the Active Treatment Period to ≥ 3 x the baseline value or a serum creatinine of ≥ 4.0 mg/dL (353.6 µmol/L, Kidney Disease Improving Global Outcomes [KDIGO] March 2012) that is confirmed by repeat assessment by the central laboratory.

9.1.3.2 Drug Hypersensitivity

Drug hypersensitivity will be as assessed by the Investigator. Assessments should be performed as described in Section 8.2.3.6.

9.1.3.3 Potential Hy's Law Case

Potential Hy's Law cases for this purpose will be defined as elevation in ALT > 3 x ULN with a concomitant increase in total bilirubin that is > 2 x ULN that is confirmed by repeat assessment by the central laboratory. AST is not being used in this definition since there may be increases in AST that are due to the index AMI event. Hy's Law is defined as an elevation in AST or ALT > 3 x ULN with a concomitant increase in total bilirubin that is > 2 x ULN without initial findings of cholestasis (elevated alkaline phosphatase), and with no other

reason found to explain the combination of these increased AST/ALT and total bilirubin findings (Guidance for Industry: Drug-induced Liver Injury: Premarketing Clinical Evaluation 2009). Additional assessments should be performed as described in Section 8.2.2.

9.1.3.4 Hemolysis

Hemolysis will be defined as a decrease in hemoglobin during the Active Treatment Period of ≥ 2 g/dL from baseline that is not explained by overt blood loss. Additional assessments should be performed as described in Section 8.2.3.7.2.

9.1.3.5 Bleeding Events

Bleeding events will be assessed according to the BARC definition for bleeding (see Appendix IV).

9.2 SEVERITY OF ADVERSE EVENTS

The severity of each AE (ie, nonserious and serious AEs) is to be assessed by the Investigator using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria as follows:

NCI Grade	Definition
Grade 0	Grade 0 is universally defined as absence of AE or within normal limits or values.
Grade 1	An AE that is asymptomatic; or involves mild or minor symptoms; or is of marginal clinical relevance; or consists of clinical or diagnostic observations alone; or for which intervention is not indicated; or for which only non-prescription intervention is indicated.
Grade 2	An AE for which only minimal, local, or noninvasive intervention (eg, packing, cautery) is indicated; or that limits instrumental activities of daily living (ADLs, eg, shopping, laundry, transportation or ability to conduct finances).
Grade 3	An AE that is medically significant but not life-threatening; or for which inpatient care or prolongation of hospitalization are indicated; or that is an important medical event that does not result in hospitalization, but may jeopardize the patient or may require intervention either to prevent hospitalization, to prevent the AE from becoming life-threatening or causing death; or that is disabling; or that results in persistent or significant disability, incapacity, or limitation of self-care activities of

NCI Grade	Definition
	daily living (ADLs, eg, getting in and out of bed, dressing, eating, getting around inside, bathing, or using the toilet).
Grade 4	An AE that has life-threatening consequences; for which urgent intervention is indicated; that puts the patient at risk of death at the time of the event if immediate intervention is not undertaken; or that causes blindness or deafness.
Grade 5	The termination of life as a result of an AE.

ADLs = activities of daily living; AE = adverse event; NCI = National Cancer Institute

Note: Definitions provided here correspond to: NCI Common Terminology Criteria for Adverse Events V4.0.

If an AE is reported that is not part of the CTCAE criteria, the following criteria will be used:

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 ADLs.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADLs, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual ADLs, or significantly affects clinical status, or may require intensive therapeutic intervention.

ADLs = activities of daily living; AE = adverse event

Note: definitions are based on the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Severity Intensity Scale for Adverse Event 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).

9.4 OBSERVATION PERIOD FOR ADVERSE EVENTS

The observation period for AE (and SAE) reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish with the end of study visit (Visit 8).

If the Investigator becomes aware of an SAE that has started 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).

9.5 ADVERSE EVENT REPORTING

At each clinical evaluation, the Investigator (or medically-qualified delegate) will determine whether any AEs have occurred. Adverse events will be recorded in the AE page 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 end of study visit, the AE will continue to be followed up until resolution, stabilization.

If, during the study period, a subject presents with a preexisting condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History section of the eCRF.

For AE reporting, the study period is defined as that time period from the signature of the informed consent form (ICF) through Visit 8. Therefore, events that occur before the initial screening visit will be recorded in the medical history and events that occur after the signing of the ICF will be recorded as an AE.

9.5.1 Adverse Events of Special Interest

9.5.1.1 Stage 3 Acute Kidney Injury

Any elevation in serum creatinine of ≥ 3 x the baseline value or a serum creatinine of ≥ 4.0 mg/dL (353.6 µmol/L) that is confirmed by repeat assessment by the central laboratory should be reported as an SAE as described in Section 9.6. In addition, the increased value should be confirmed by repeat assessment by the central laboratory and followed until resolution or stabilization.

9.5.1.2 Drug Hypersensitivity Reaction

If a drug hypersensitivity reaction is suspected, it should be reported as an AE as described in Section 9.1. Assessments should be performed as described in Section 8.2.3.6.

9.5.1.3 Potential Hy's Law Case

An elevation in ALT > 3 x ULN with a concomitant increase in total bilirubin that is > 2 x ULN should be should be reported as an SAE as described in Section 9.6 as this could be an indicator of a potential Hy's Law case. See Section 9.1.3.3 for definition of Hy's Law. Additional assessments should be performed as described in Section 8.2.2.

9.5.1.4 Hemolysis

Hemolysis as defined in Section 9.1.3 should be reported as an AE as described in Section 9.1. Additional assessments should be performed as described in Section 8.2.3.7.2.

9.5.1.5 Bleeding Events

Bleeding events should be reported as AEs (see Sections 3.6.4 and 9.1) and the Bleeding Event eCRF page must be completed for each suspected bleeding event.

9.6 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).

All SAEs that occur during the course of the study, whether or not causally related to the investigational product, must be reported and 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 that 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 immediately (within 24 hours of the Investigator becoming aware of the event) in the clinical study database in the same manner as other SAEs.

Any SAE that occurs after the end of study visit that is considered to be causally related to investigational product must be **immediately (ie, within 24 hours of the Investigator becoming aware of the event) reported to the sponsor**.

If access to the clinical database is not available (eg, system or internet access problem, or the clinical study database is locked), a handwritten SAE report must be completed, signed and dated by the Investigator and sent to CSLB Global Clinical Safety and Pharmacovigilance via facsimile or email.

If and/or when the system becomes available post outage, the SAE must be entered in to the clinical study database immediately.

9.6.1 Requirements for Immediate Reporting of Serious Adverse Events

The minimum reporting requirements for immediate entry of SAEs in the eCRF include:

- Identifiable subject.
- Suspected medicinal product and / or procedure.
- Event term.
- Identifiable reporting source.

In addition, the Investigator must:

- Report all SAEs to the relevant IRB / IEC within the timeframe specified by the IRB / IEC.
- Enter relevant 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.

If the minimum requirements for reporting are fulfilled, the Investigator should not wait to receive additional information to fully document the event before entering the information into the clinical study database.

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 cases of death, the Investigator should supply CSLB and the IRB / IEC (as applicable) with any additional information as it becomes available (eg, autopsy reports). When submitting medical reports to CSLB, the subject should be identified only by their subject identification number and study number.

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 9.9.

9.7 OTHER SIGNIFICANT EVENT REPORTING

9.7.1 Overdose

Details (ie, volume, location of infusions, infusion rate) of overdose of investigational product or any concomitant therapy must be recorded in the eCRF. Any overdose that is considered by the Investigator to be medically significant (ie, occurs in association with an event and meets any seriousness criteria) must be entered as an SAE (see Section 9.5.1). An overdose that does not result in any adverse signs or symptoms should not be considered an AE (see Section 9.1.1).

9.7.2 Pregnancy and Lactation

A female subject or female partner of a male subject who becomes pregnant while participating in the study, or up to and including 3 months after the last dose of investigational product, must notify the Investigator immediately.

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. If the female subject is in the Active Treatment Period of the study, her participation will be discontinued and the procedure for discontinuation of a subject will be followed, as described in Section 4.1.4). Every effort will be made to ensure that the relevant safety assessments for early termination Visit 7 are completed (telephone documentation is allowed).

CSLB must be notified within 5 days of the Investigator becoming aware of the pregnancy.

Whenever possible, a pregnancy in a subject or in a female partner of a male subject exposed to investigational product should be followed to term so as 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.

If the outcome of the pregnancy meets the criteria for classification as an SAE (eg, spontaneous abortion, stillbirth, neonatal death or congenital anomaly) then the Investigator should follow the procedure for reporting an SAE (Section 9.6.1).

9.8 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.

9.9 FOLLOW-UP OF ADVERSE EVENTS

Every effort should be made to follow-up subjects who continue to experience an AE, AE of special interest, or an SAE on completion of the study until either the AE resolves or stabilizes. All follow-up information (and attempted follow-up contacts) should be documented in the subject's medical records. Relevant details of the subject's progress should also be entered in the eCRF.

10. STATISTICS

10.1 SAMPLE SIZE ESTIMATION

This is a randomized, placebo-controlled, multi-dose safety study in subjects with moderate RI and AMI. Subjects are to be randomized to CSL112 or placebo treatment in a 2:1 ratio. The co-primary endpoints are:

- Renal SAEs (defined as any SAE with a MedDRA PT included in the Acute Renal Failure narrow SMQ or a PT of renal tubular necrosis, renal cortical necrosis, renal necrosis, or renal papillary necrosis), and
- AKI, defined as an absolute increase in serum creatinine from baseline of ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period that is sustained upon repeat

measurement by the central laboratory no earlier than 24 hours after the elevated value. If no repeat value is obtained [due, for example, to loss of follow-up or protocol violation], a single serum creatinine value that is increased from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period would also fulfil the definition of AKI. Baseline for determination of AKI is defined as the pre-infusion central laboratory serum creatinine level on Study Day 1.

With a sample size of 81 (54 active: 27 placebo), the study will detect with 80% probability a treatment-emergent event with a frequency of 3% in the active group and 2% overall. A total of 81 subjects, 27 placebo and 54 CSL112, is planned for this study to meet regulatory considerations for treatment-emergent renal event characterization; it is not powered for statistical testing of the co-primary endpoints.

10.2 STUDY POPULATIONS

10.2.1 Screened Population

The Screened Population will comprise all subjects who provided written informed consent to undergo study screening procedures.

10.2.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will comprise all subjects in the Screened Population who were randomized to 1 of the 2 treatment groups. This population will be analyzed using the treatment to which the subject was randomized regardless of the treatment actually received.

10.2.3 Safety Population

The Safety Population will comprise all subjects in the ITT Population who received at least a partial dose of investigational product, and will be based on the actual treatment received.

10.2.4 Pharmacokinetic Population

The PK Analysis Population will comprise all subjects in the Safety Population who have at least 1 measurable plasma concentration of apoA-I or PC.

10.2.5 CCI

CCI

10.3 STATISTICAL ANALYSES AND METHODS

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

10.3.1 Subject Disposition, Demographics, and Baseline Characteristics

The number of subjects who were screened, failed screening, randomized, treated, and completed the study will be presented in summary tables by treatment group and overall. The reason for discontinuing study treatment or withdrawal from the study will be summarized and listed by subject.

Demographics and baseline characteristics of subjects in the Safety Population will be summarized using descriptive statistics by treatment group and overall. Continuous data will be summarized by descriptive statistics and categorical data will be summarized by frequencies and proportions. Age will be described as both a continuous and a categorical variable. Supportive data will be listed by subject.

10.3.2 Safety Analyses

10.3.2.1 Co-Primary Endpoints

For the co-primary safety endpoints of treatment-emergent renal SAEs and AKI events, incidence rates will be based on the number of subjects with at least 1 occurrence of the event

of interest; eg, a subject with 2 treatment-emergent renal SAEs will be counted once. Baseline for determination of AKI is defined as the pre-infusion central laboratory serum creatinine level from Study Day 1. Acute kidney injury events will be identified using central laboratory results. Treatment-emergent is defined as occurring at or after the start of the first infusion. The difference in incidence rates will be computed by subtracting the rate in the placebo arm from the incidence rate in the CSL112 arm so that a positive difference indicates a higher incidence rate in the CSL112 arm. For each co-primary endpoint, Newcombe-Wilson 2-sided 95% confidence intervals around the difference in incidence rates will be calculated if at least 1 event occurs. Otherwise, an exact, 1-sided, upper 97.5% confidence interval will be reported for the incidence rate in each treatment arm.

A sensitivity analysis of the renal SAE co-primary endpoint will use independently adjudicated results and the same methods as the primary study analysis. A sensitivity analysis of the AKI co-primary endpoint will use local laboratory results and the same methods as the primary study analysis.

Acute kidney injury rates will be compared among subjects whose dosing eligibility was determined in part based on serum creatinine determinations performed 12 to 24 hours after radiographic contrast exposure versus those whose dosing eligibility was determined in part based on serum creatinine determinations performed 48± 6 hours after radiographic contrast exposure. If data on subjects with serum creatinine determinations performed 12 to 24 hours after radiographic contrast are insufficient to perform this analysis, an analysis comparing the AKI rates among subjects whose dosing eligibility was determined in part based on serum creatinine determinations performed 12 to 48 hours after radiographic contrast exposure versus those whose dosing eligibility was determined in part based on serum creatinine determinations performed > 48 hours after radiographic contrast exposure will be performed. For either analysis, the difference in placebo-corrected rates between the 2 time-period subgroups will be calculated, along with a 2-sided 95% confidence interval.

All primary endpoint analyses will use the Safety population.

10.3.2.2 Other Safety Analyses

All subjects in the Safety Population will be evaluated for safety. Treatment group classification will be according to the treatment actually received. Treatment-emergent AEs will be summarized by treatment, grade, relationship to study treatment, and seriousness. Changes from baseline (pre-infusion on Study Day 1) in clinical laboratory assessments, vital sign measurements, ECG interval measurements, immunogenicity, and proteinuria will be summarized by treatment and changes of potential clinical significance will be identified. Descriptive statistics will be used to summarize the exposure to study treatment and the safety assessments. Non-laboratory value-based AEs of special interest (hypersensitivity and bleeding events; Section 9.1.3) will be summarized and listed. The summary of bleeding AEs of special interest will use those adjudicated by the CEC using BARC criteria. Bleeding events will be listed separately by source (Investigator reported and CEC adjudicated). Laboratory value-based AEs of special interest (AKI, hemolysis, and potential Hy's Law cases) will be reported using serum biochemistry and hematology laboratory values.

10.3.3 Pharmacokinetic CCI Analyses

Measured plasma concentrations of apoA-I and PC, and baseline-corrected concentrations (ie, change from baseline) will be listed and summarized by time point. Plasma PK parameters for apoA-I and PC will be summarized descriptively. The following parameters will be calculated:

- Maximum concentration in plasma (C_{max})
- Accumulation Ratio

Nonlinear mixed effects modeling will be performed to assess the PK data for apoA-I and PC. This population-based approach will be used to explore and quantify clinically relevant covariates such as age, sex, and renal function on population PK parameters.

CCI

10.3.4 Safety Review

An external program level DSMB will independently review safety data after every 6 subjects have received 2 infusions of investigational product and have pre-infusion safety data available before the third infusion at Visit 5. These reviews will continue until at least 60 subjects (approximately 75% of subjects) complete Visit 5. In addition, the independent DSMB will have interim safety reviews when: (1) approximately 25% of subjects have completed the Active Treatment Period (Visit 7), (2) approximately 50% of subjects have completed Visit 5, and (3) approximately 50% of subjects have completed the Active Treatment Period (Visit 7). At all planned reviews the DSMB will assess for any safety signal that has emerged and that would warrant a change in the conduct of the study or provide recommendations regarding subsequent dosing and/or study progression/stopping. The DSMB will also be convened to review all available data if 1 or more of the study level stopping rules is/are met (see Section 3.6.2)

If any of the safety stopping rules is met, or other safety concerns are identified, at these reviews, continuation of the study without alteration should be questioned as it may be an early indication of an unacceptable safety profile in the broader population. The DSMB may recommend a change to the protocol to ameliorate any safety concerns.

10.3.5 Other Analyses

A population PK analysis to explore the relationship between the PK of apoA-I and PC and demographic and clinical features of the subject population will be detailed and reported separately.

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[redacted]

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11. QUALITY ASSURANCE

Before a site enrolls subjects, the Study Monitor will conduct a Site Initiation Visit. The purpose of the Site Initiation Visit is to provide the staff with training on the following:

- Study protocol procedures to ensure high quality and consistent data collection
- Maintenance of the Investigator site files
- Responsibilities of site staff and Investigators, under ICH GCP, to ensure that the rights and well-being of subjects are protected.

Representatives of the sponsor will visit all study sites periodically to assess the data quality, site conduct and study integrity. On site, they will review study data and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable. Further information regarding data quality assurance is found in Section 13.5.2.

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 immediately notify the Investigator of an 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 and will await approval before study start.

This study will be conducted under an FDA IND application 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 (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

The principles of informed consent in the Declaration of Helsinki must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB / IEC. Subjects, their relatives (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

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 IDENTIFICATION AND 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

It is CSLB policy that persons who participate in CSLB's clinical studies should be no worse off for their having been involved in the study. These persons include the subjects / volunteers, the Investigator, the hospital and the IRB / IEC.

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 Agreement for the study (see Section 13.1).

13. ADMINISTRATIVE CONSIDERATIONS

13.1 CLINICAL TRIAL 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 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 Medical Monitor 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 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 subjects who have been entered in the study deviate from the IRB / IEC -approved study protocol.

If a major protocol deviation (ie, a deviation that could have a significant effect on the subject's safety, rights, or welfare and / or on the integrity of the study data) occurs, the Investigator must notify CSLB and the appropriate IRB / IEC as soon as possible or as per local requirements.

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 constitute source 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 there is prior agreement that the eCRF is the 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. CSLB's study monitor will perform this function.

After 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

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 the 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.

After 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 it. The Investigator at each study site will advise the IRB / IEC overseeing the study at their site.

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.

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Appendix I:Calculation of Estimated Glomerular Filtration Rate by the Chronic Kidney Disease Epidemiology Collaboration Equation

eGFR = 141 X min(Scr/κ,1)α X max(Scr/κ,1)-1.209 X 0.993Age X 1.018 [if female] X 1.159 [if black]) or if subject is receiving dialysis (Levey et al, 2009; Stevens et al, 2010)

An eGFR calculator can be found on the National Kidney Foundation's website at the following address: http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm

Estimated glomerular filtration rate will be determined automatically via IRT at the randomization visit.

Appendix II: Third Universal Definition of Myocardial Infarction

Definition of myocardial infarction

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL)or a rise of cTN values >20% of the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic finding consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves of new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

Reference:
Thygesen K, Alpert J, Jaffe A, et al. Third Universal Definition of Myocardial Infarction. Circulation. 2012;126:2020-35.

Appendix III: Killip Classification

- **Killip class I** includes individuals with no clinical signs of heart failure.
- **Killip class II** includes individuals with rales or crackles in the lungs, an S_3 heart sound, and elevated jugular venous pressure.
- **Killip class III** describes individuals with frank pulmonary edema.
- **Killip class IV** describes individuals in cardiogenic shock or hypotension (measured as systolic blood pressure lower than 90 mmHg), and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating).

Reference:

Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit – a two year experience with 250 patients. Am J Cardiol. 1967;20:457-64.

Appendix IV: Assessment of Bleeding Events by Bleeding Academic Research Consortium (BARC) Definition for Bleeding

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least 1 of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

- Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL[a] (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b

- Overt bleeding plus hemoglobin drop ≥ 5 g/dL[a] (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
  Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4: CABG-related bleeding :

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or PRBCs within a 48-h period[b]
- Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG = coronary artery bypass graft h = hour; PRBCs = packed red blood cells

a. Corrected for transfusion (1 U PRBCs or 1 U whole blood = 1 g/dL hemoglobin).

b. Cell saver products are not counted.

NOTE: Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

Reference:
Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials. A consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736-47.