STATISTICAL ANALYSIS PLAN (SAP)

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

Investigational Medicinal Product: CSL112

Protocol Number: 3001

Version: 4.0

Version Date: 11 JANUARY 2024

Sponsor:

CSL Behring LLC (CSLB)

[redacted]

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1 Modification History

Version	Effective Date	Author of Modification	Reason for Change
1.0	27 February 2018		N/A – First Version
2.0	10 September 2019	PPD	1. Modification of the primary efficacy endpoint from (CVD, MI Type 1, or Stroke) to (CVD, MI, or Stroke)), to include all MI types. 2. Replace planned sensitivity analysis of the primary efficacy endpoint including all MI types with secondary endpoint, time to first occurrence of CV death, Type 1 MI, or stroke from the time of randomization through day 90, 180, and 365 3. Add an exploratory endpoint for time to first MI by type according to universal definition from the time of randomization through 90 days 4. Interim analysis for efficacy at 70% information fraction – add clarification that this interim analysis will not be conducted if the expected timing of the IDMC review of the 70% interim analysis is

Version	Effective Date	Author of Modification	Reason for Change
			less than 2 months prior to the anticipated completion of study enrollment 5. Sample size re-estimation will be capped at 20600 subjects even if the total number of events for the primary outcome is less than the targeted 1004 events. 6. Minor changes to correct typographical errors
3.0		PPD	1. Add a Randomized Analysis Set to distinguish from the ITT Analysis Set which may exclude sites due to potential study misconduct 2. Update to address COVID-19 impact on analysis 3. Update estimands associated with the primary objective 4. Define PK and PD Analysis Sets 5. Add exploratory endpoints for primary MACE, CV Death, and all-cause death through the end of study 6. Add text regarding interpretation of subgroups in Section 10 and in Appendix 15.4

Version	Effective Date	Author of Modification	Reason for Change
			7. Add a tipping point analysis for key secondary endpoint MACE through 365 days 8. Add text to describe suspected adverse drug reactions and local tolerability reactions 9. Represent the threshold and units for AESI of AKI in SI units (µmol/L) instead of conventional units (mg/dL) 10. Provide derivation for PK parameters 11. Remove the following appendices as information contained in them is likely to change over the course of the study. The information previously included in the appendices will be maintained in study files outside of the SAP. A description of the process in Section 9.4 replaces Appendices 15.5 and 15.6 and Section 11.2 replaces Appendix 15.8: a. 15.3 – List of tables, listings, and figures b. 15.5 – Identification of statins by dose and intensity c. 15.6 - WHO Drug Codes

Version	Effective Date	Author of Modification	Reason for Change
			d. 15.7 – List of preferred terms within SMQs e. 15.8 – Preferred terms for adverse events of special interest f. 15.9 – Displays conventions g. 15.10 - Display numbering Add clarifying text (multiple locations)
4.0	11 January 2024	PPD	1. Section 9.1: a. Derivation of last MACE ascertainment date used for censoring in efficacy analysis b. Definition of a completed visit c. Definition of primary endpoint completion status, Day 180 completion status and study completion status d. Derivation of vital status e. Delete text regarding the inclusion of last dose date and total number of infusions to be included in the listing of IP discontinuation due to revision of listing format.

[redacted]

Version	Effective Date	Author of Modification	Reason for Change
			2. Section 9.5 - Define post-index MI hospitalizations 3. Section 10.1 and 10.2.2 – clarifying text regarding censoring Section 10.4: a. Clarifying text on the derivation of exploratory endpoint "total occurrence of re-hospitalization for CV events. b. Clarifying text to indicate planned analysis of time-to-event endpoints at additional time points not explicitly listed 5. Section 11.2.2 – addition of a supporting table of potential hepatic injury including both central and local lab results Section 11.3.2 -clarifying text on local tolerability reactions 6. Section 11.6.1 – clarify that only central lab results to be used for analysis of laboratory data

Version	Effective Date	Author of Modification	Reason for Change
			with the exception of potential hepatic injury. 8. Section 11.6.2.1 – clarifying text that renal function to be summarized only during the active treatment period 9. Section 11.7.4 – Clarifying text to describe the planned analysis and shift table

2 List of Abbreviations

Abbreviation	Definition
ACEI	Angiotensin Converting Enzymes Inhibitors
ACS	Acute Coronary Syndrome
ACD	All-cause death
ADaM	Analysis Data Model
AE	Adverse Event
apoA-I	Apolipoprotein-I
ARB	Angiotensin II Receptor Blockers
ATC	Anatomical Therapeutic Chemical
CAR	Censored-at-random
CBC	Complete Blood Count
CCU	Cardiac Care Unit
CEC	Clinical Events Committee
CI	Confidence Interval
CSLB	CSL Behring
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Cardiovascular
DILI	Drug Induced Liver Injury
EAIR	Exposure-Adjusted Incidence Rate
EMA	European Medicines Agency
FMC	First Medical Contact
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IP	Investigational Product
IR	Incidence Rate
ITT	Intent-to-Treat
LLN	Lower Limit of Normal
MACE	Major Adverse Cardiac Event

Abbreviation	Definition
MedDRA	Medical Dictionary for Medical Affairs
MI	Myocardial Infarction
mITT	Modified Intent-to-treat
NSTEMI	Non-ST-segment elevation Myocardial Infarction
PC	Phosphatidylcholine
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamics
PK	Pharmacokinetics
RI	Renal Impairment
SAE	Serious Adverse Event
SAH	Subarachnoid hemorrhage
SAP	Statistical Analysis Plan
SDAC	Statistical Data Analysis Center
SMQ	Standard MedDRA Query
SOC	System Organ Class
STEMI	ST-segment elevation Myocardial Infarction
TBili	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
VAS	Visual Analog Scale

3 Purpose

This statistical analysis plan (SAP) provides a detailed description of the planned statistical analyses for the final analysis of the study CSL112_3001 to support the Clinical Study Report and regulatory submission. Mock tables, listings, and figures shells are provided in separate supporting documents.

This SAP complies with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Topic E9 - Statistical Principles for Clinical Trials and E9 (R1) – Addendum on Estimands and Sensitivity Analysis in Clinical Trials. It is based upon the following study documents:

Clinical Study Protocol (CSP) Amendment 1 dated 10 September 2019

Electronic Case Report Form (eCRF) dated 23 April 2021

The "Guideline on Missing Data in Confirmatory Clinical Trials" [EMA, 2010] and the “National Research Council Panel on Handling Missing Data in Clinical Trials” [National Research Council, 2010] are considered to be relevant for analysis methodologies for missing data for the primary efficacy comparison.

All decisions regarding the final analysis of the study results, as defined in this SAP, will have been made prior to database lock of the study data.

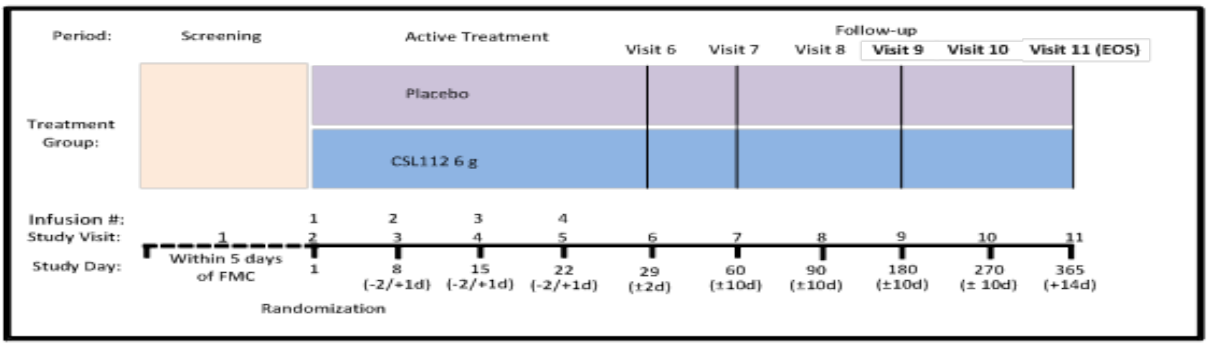
4 Study Design

4.1 Study Design

This is a phase 3 multicenter, double-blind, randomized, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of CSL112 on reducing the risk of Major Cardiac Adverse Event (MACE) in subjects with Acute Coronary Syndrome (ACS) (diagnosed with ST-segment elevation myocardial infarction [STEMI] or non-ST-segment elevation myocardial infarction [NSTEMI]). CSL112 is a novel intravenous formulation of apolipoprotein A-1 (apoA-I). The primary endpoint is defined as time to first occurrence of any component of composite MACE, defined as cardiovascular (CV) death, myocardial infarction (MI), or stroke from the time of randomization through 90 days. The study design is based upon the hypothesis that compared to placebo, CSL112 will achieve a 20% relative risk reduction (hazard ratio = 0.80) in the primary endpoint over 90 days of follow-up after randomization.

Subjects will be randomized to CSL112 or matching placebo in a 1:1 allocation ratio, stratified by index MI type (STEMI vs. NSTEMI), management of index MI (percutaneous coronary intervention [PCI] or medically managed), and region (North America, Latin America, Western Europe, Central and Eastern Europe, and Asia-Pacific). For a list of countries within each region and estimated number (%) of subjects expected to be recruited within each region, see Appendix 15.3.

Figure 4–1 Study Schema



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

The study consists of a screening period, an active treatment period, and a follow-up period. The screening period will end within five days of first medical contact (FMC); the active treatment period ranges from the day of randomization through Day 29 (includes Visits 2 through 6) with the follow-up period lasting from Day 30 through Day 365 post-randomization (includes Visits 7 through 11).

Interim analyses for futility and efficacy will be conducted at scheduled intervals by the Independent Data Monitoring Committee (IDMC). Three planned interim analyses will be performed following observation of approximately 30%, 50%, and 70% of the event target for the primary MACE endpoint based on CEC confirmed events; ie positively adjudicated events. The first and second interim analyses will be for futility only while the third interim analysis will be for efficacy only. As part of the IDMC charter, criteria will be specified for early termination of the study for futility and efficacy. Based on event accrual, if the expected timing of the IDMC review of the 70% interim analysis is less than 2 months prior to the anticipated completion of study enrollment, the 70% interim analysis for efficacy will not be conducted.

During the course of study, the IDMC will conduct safety reviews periodically as well as assess safety with respect to hepatic and renal function when the first 20% of enrolled subjects have completed Visit 6/Study Day 29. In addition, the IDMC will review renal function for those subjects dosed within 12-<48 hours after angiography contrast administration. In-depth information on the planned interim analyses is provided in SAP Section 4.6.

The study will conclude at least 365 days after the last subject is randomized.

4.2 Objectives and Endpoints

Primary Objective	**Primary Endpoint**
The primary objective of this study is to evaluate the efficacy of CSL112 on reducing the risk of MACE, (CV death, MI, or stroke) from the time of randomization through 90 days in subjects with ACS (diagnosed with STEMI or NSTEMI)	Time to first occurrence of any component of composite MACE, defined as CV death, MI, or stroke from the time of randomization through 90 days The primary endpoint will include all MIs.
Key Secondary Objectives	**Key Secondary Endpoints**
1. To evaluate the efficacy of CSL112 on reducing the total number of hospitalizations for coronary, cerebral, or peripheral ischemia 2. To evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) through 180 days and 365 days in subjects with ACS (diagnosed with STEMI or NSTEMI)	1. Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days 2. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 180 days. 3. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 365 day

Other Secondary Objectives	Other Secondary Endpoints
1. To further evaluate the efficacy of CSL112 on reducing the risk of MACE (CV death, MI, or stroke) and all-cause death in subjects with ACS (diagnosed with STEMI or NSTEMI)	1. Time to first occurrence of each individual component of the composite primary efficacy endpoint at 90 days a. CV death b. MI c. Stroke 2. Time to occurrence of CV death, Type 1 MI, or stroke from the time of randomization through days 90, 180, and 365 3. Time to occurrence of all-cause death from the time of randomization through 365 days
2. To evaluate the safety of CSL112 in subjects with ACS (diagnosed with STEMI or NSTEMI)	1. Adverse events 2. Changes in Clinical Laboratory Assessments
Exploratory Objectives	**Exploratory Endpoints**
1. To evaluate the efficacy of CSL112 on reducing the rate of hospitalization for coronary, cerebral, or peripheral ischemia	1. Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 30 days
2. To further explore the effect of CSL112 on the risk of MACE (CV death, MI, or stroke), non-CV death and severe coronary ischemia requiring urgent revascularization	1. Time to first occurrence of CV death, MI, stroke, or severe coronary ischemia requiring urgent revascularization from the time of randomization through 90 days

	2. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 30 and 60 days 3. Time to first MI by type according to universal definition from the time of randomization through 90 days 4. Time to occurrence of CV death from the time of randomization through 365 days 5. Time to occurrence of non-CV death from the time of randomization through 365 days 6. Total occurrence of rehospitalization for CV events and all-cause death from the time of randomization through 90 days 7. Total occurrence of all-cause death, MI, and stroke from the time of randomization through 90, 180, and 365 days 8. Total occurrence of CV death, MI, and stroke from the time of randomization through 90, 180, and 365 days
3. To assess the impact of CSL112 on medical resource utilization and quality of life	1. Medical resource utilization through days 90 from the time of randomization: a. Number of hospitalizations b. Length of hospital stay c. Number of critical care unit or intensive care unit days d. Select procedures / surgeries related to hospitalization for coronary, cerebral, or peripheral ischemia

	e. Discharge to: home with additional care, home without additional care, rehabilitation, and skilled nursing home following hospitalization for coronary, cerebral, or peripheral ischemia 2. Change in EQ-5D-3L data from baseline to Day 90
4.To evaluate the Pharmacokinetic (PK)/Pharmacodynamic (PD) characteristics of CSL112	1. Pharmacokinetic endpoints will include the following: a. Baseline-corrected plasma apoA-I concentrations b. Baseline-corrected plasma Phosphatidylcholine (PC) concentrations c. Concentration in plasma at the end of infusion for apoA-I and PC d. Accumulation ratio for apoA-I and PC 2. Pharmacodynamic endpoints include the following: a. Total cholesterol efflux b. ABCA1-dependent efflux c. ABCA1-independent efflux

4.2.1 Primary Study Hypothesis

The primary study hypothesis is to test whether treatment with CSL112 is superior to placebo as measured by the time to first occurrence of any component of composite MACE during the time from randomization through 90 days. The components of the primary composite MACE include CV death, MI, or stroke. All adjudicated MIs from the time of randomization through

90 days will be included in the primary endpoint. Statistical analysis will be based on events independently adjudicated and confirmed by the blinded, CEC. Superiority will be assessed using the Intent-to-Treat (ITT) Analysis Set and a 1-sided type I error rate of 0.025. A covariate-adjusted Cox regression model including fixed effects for treatment, stratification factors (region, index MI type, index MI management), age, diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and management will be used to obtain point and interval estimates of the hazard ratio and a 1-sided Wald *P* value for the treatment effect to test the null hypothesis.

The primary hypothesis of the study is symbolically expressed as shown below:

H_{01}: Hazard ratio (λ_t / λ_c) ≥ 1.0
H_{11}: Hazard ratio (λ_t / λ_c) < 1.0

Where: λ_t = hazard rate of MACE in the CSL112 arm and λ_c = hazard rate of MACE in the placebo arm. The interpretation of the hazard ratio under the null hypothesis H_{01} is that the hazard of MACE on CSL112 is worse than or no different from placebo whereas the alternative hypothesis H_{11} reflects a reduction in the hazard of MACE attributable to CSL112.

4.2.2 Key Secondary Endpoint Hypotheses

The key secondary objective is evaluated based on three key secondary endpoints. The formal hypothesis-testing framework is designed to include the key secondary endpoints and to demonstrate the superiority of CSL112 over placebo.

The null and alternative hypotheses for each of the three key secondary efficacy endpoints are stated below:

Superiority:

H_{02}: Rate ratio (CSL112 / Placebo) of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days ≥ 1.0
H_{12}: Rate ratio (CSL112 / Placebo) of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 90 days < 1.0

H_{03}: Hazard ratio (CSL112 / Placebo) for time to first occurrence of CV death, MI or stroke from the time of randomization through 180 days ≥ 1.0
H_{13}: Hazard ratio (CSL112 / Placebo) for time to first occurrence of CV death, MI or stroke from the time of randomization through 180 days < 1.0

H_{04}: Hazard ratio (CSL112 / Placebo) for time to first occurrence of CV death, MI or stroke from the time of randomization through 365 days ≥ 1.0
H_{14}: Hazard ratio (CSL112 / Placebo) for time to first occurrence of CV death, MI or stroke from the time of randomization through 365 days < 1.0

The interpretation of the null hypothesis associated with the total number of hospitalizations for cerebral, coronary, or peripheral ischemia is that the mean rate of hospitalizations on the CSL112 arm is equal to or higher than placebo while the alternative hypothesis states that the mean rate of hospitalizations is lower in subjects treated with CSL112 compared to placebo.

The interpretation of the null and alternative hypotheses for the time to first occurrence of CV death, MI or stroke from the time of randomization through 180 and 365 days is similar to that of the primary efficacy endpoint; ie, the null hypothesis is positing a similar or worse MACE hazard to 180 and 365 days on CSL112 relative to placebo while a reduced hazard of event is assumed under the alternative hypothesis.

4.3 Study Treatments

The test and control treatment groups in the study are CSL112 (6 g dose) and placebo. Study interventions will be administered on top of evidence-based medical therapy. An approximate total volume of 170 mL will be intravenously infused over a 2-hour time period for either the active or placebo arm. The investigational product is scheduled to be administered once weekly for 4 consecutive weeks.

4.4 Randomization Procedures and Blinding

Subjects, who have provided written informed consent, completed the screening procedures and met entry criteria, will be randomized in a 1:1 ratio to CSL112 or placebo. The randomization schedule will be blocked and stratified by the type of index MI (STEMI or NSTEMI), whether the index MI is managed with PCI or medically managed, as well as region. The 5 levels of region include North America, Latin America, Western Europe, Central and Eastern Europe, and Asia Pacific. See Appendix 15.3 for a list of regions, countries, anticipated recruitment rate for each region. Treatment assignment will occur within each of 20 strata with the goal of achieving treatment group balance at stratum level.

Treatment assignment to subjects will occur centrally, at the regional level, without regard to country or site. A web-based Interactive Response Technology (IRT) will be used to carry out the process of randomization.

The scope of the randomization schedule, including the fixed block size, will be specified by the CSLB study statistician or designee with the corresponding schedule generated by the IRT external service provider for the study. An initial dummy schedule will be reviewed and approved by the CSLB statistician or designee before the master list is generated using a different random seed. A dummy schedule will be used in programs for generating dry run tables, listings, and figures prior to database lock and study unblinding.

Blinding:

The study is designed to be double-blind with investigational site staff, subjects, and sponsor blinded to treatment assignment. Designated unblinded site personnel will be responsible for preparing the investigational product for infusion.

In order to ensure the integrity of blinded data, the investigator will not obtain a lipid panel during the active treatment period as the results may unblind treatment assignment.

The study will conclude at least 365 days after the last subject is randomized. Treatments will be formally unblinded only after database lock has been declared. However, if it becomes necessary to identify the treatment assignment for medical management of a study subject, in case of a medical emergency, the investigator may do so within the IRT system. The investigator is required to fully document the reason for unblinding in the source documents.

4.5 Determination of Sample Size

The sample size calculation was performed using East 6.4 and is based upon the hypothesis that compared to placebo, CSL112 will achieve a 20% relative risk reduction (hazard ratio of 0.80) in the primary endpoint over 90 days of follow up from the time of randomization. With this design, the total number of events required is 1004 and the total estimated sample size is 17,400 subjects.

The following assumptions were made in calculating the sample size:

- A 90-day MACE event rate of 6.4% in the placebo arm based on Duke Clinical Research Institute ACS Clinical Trial Database
- A hazard ratio (CSL112: Placebo) of 0.8 under the alternative hypothesis and 1.0 under the null hypothesis
- A 1:1 allocation scheme

- Approximately 91.9% chance of successfully claiming superiority in the presence of a true underlying difference
- A 2.5% chance of erroneously claiming superiority in the presence of no true underlying difference, ie, 1-sided 2.5% significance level
- Recruitment time of 38 months
- A fixed duration of follow-up equal to 90 days for primary efficacy assessment
- 3 interim analyses (at 30%, 50%, and 70% of expected confirmed event target) and 1 final analysis; first and second interim analyses will be for futility only while the third interim analysis will be for efficacy only
- Futility bounds determined on the hazard ratio scale such that the lower limit of a two-sided 95% confidence interval (CI) for the hazard ratio excludes the hypothesized treatment effect; ie, a hazard ratio of 0.8
- A stopping boundary from the Rho [Kim and DeMets, 1987] family alpha-spending function with a parameter value of 16 to evaluate whether to stop early for dramatic benefit at the expected confirmed event target of 70%
- Hypothesis testing with a 1-sided log-rank test

Under these assumptions, a total of approximately 1004 adjudicated, CEC confirmed MACE events with an estimated total sample size of 17,400 subjects will afford the trial greater than 90% power to reject the null hypothesis. The target estimated number of events is also sufficient to achieve a 1-sided *P* value of 0.005 (approximate) with an observed hazard ratio of 0.85 in the primary endpoint; ie, time to first occurrence of any component of MACE (CV death, MI, or stroke). In addition, if the assumed hazard ratio is 0.85 (the minimally clinically relevant hazard ratio), 1004 events would provide at least 69% power.

A recruitment period of 38 months and study duration of 50 months are anticipated.

4.6 Planned Interim Analyses and Reviews

4.6.1 Interim Analyses

An unblinded Independent Data Monitoring Committee (IDMC) will be convened to review the accumulating efficacy and safety data. The specific responsibilities and composition of the IDMC will be outlined in the IDMC charter which is a separate document. The statistical analysis and generation of relevant output for the IDMC review will be performed by an external Statistical Data Analysis Center (SDAC) using the master randomization schedule provided by the IRT service provider.

To preserve the integrity of the study blind, the results of the interim analysis will only be known to the IDMC, and any recommendation to terminate the study would not be based solely on statistical grounds. A number of factors must be considered as part of the decision including exploring internal consistency across key subgroups, across primary and key secondary endpoints, possible differences in prognostic factors between treatment groups and taking external information into account [Ellenberg et al, 2002]. The communication process between the IDMC and the sponsor/Executive Committee will be outlined in the IDMC charter.

4.6.1.1 Interim Analyses for Futility and Efficacy

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

- There is strong evidence that CSL112 will fail to show superiority with respect to the primary MACE endpoint if the study is allowed to run to its planned completion (futility), based on whether or not the lower limit of a two-sided 95% CI for the hazard ratio excludes a value of 0.8

- There is strong evidence that CSL112 is superior to placebo with respect to the primary MACE endpoint (efficacy), based on a Rho alpha spending function with an associated parameter value of 16.

Of the 3 planned interim analyses, the first two will be for futility only while the third will be for efficacy only. The two futility interim analyses will be conducted after observation of approximately 301 (30% of the total target) and 502 (50% of the total target) confirmed MACE, respectively. The third interim analysis for efficacy will take place after observation of approximately 703 confirmed MACE (70% of the total target number of events). Based on event accrual, if the expected timing of the IDMC review of the 70% interim analysis is less than 2 months prior to the anticipated completion of study enrollment, the 70% interim analysis for efficacy will not be conducted. Events to be counted toward the interim analysis targets will be adjudicated events from patients with at least 90 days of follow-up to ensure there is adequate representation across the full 90-Day time period in the primary endpoint.

For the purpose of evaluating whether to stop the study for futility, a two-sided 95% CI for the interim hazard ratio will be calculated. If the lower limit excludes 0.8, the hypothesized treatment benefit, a conclusion of no true underlying difference in treatments will be reached.

This approach corresponds to observed hazard ratio point estimates of ≥1.003 and ≥0.953 at the first (30% of the total target number of events) and second (50% of the total target number of events) futility analyses, respectively.

This futility boundary does not represent a binding decision to stop the study should the boundary be crossed at either interim analysis. Data external to the study may also be considered.

For the purpose of evaluating whether to stop for efficacy, an alpha-spending function from the rho family, with a parameter value of 16, will be utilized. The stopping boundary for efficacy requires an approximate point estimate for the hazard ratio of < 0.753 or a 1-sided *P* value < 0.000083 assuming the interim analysis is conducted with exactly 703 events. Such a finding would provide robust and compelling evidence of treatment effect attributable to CSL112. There is a 21% chance of meeting the efficacy threshold if the true hazard ratio is 0.8. For efficacy interim analysis, the stopping boundary will be recomputed at the time of analysis using the actual number of events included in the interim analysis, and the specified alpha-spending function. Based on event accrual, if the expected timing of the IDMC review of the 70% interim analysis is less than 2 months prior to the anticipated completion of study enrollment, the 70% interim analysis for efficacy will not be conducted. If the 70% interim analysis is not conducted, an alpha adjustment will be applied as if it were conducted (ie, the alpha level for the final analysis will be 0.024999).

The statistical properties of this design are discussed below.

Table 4-1 Stopping Boundary Values

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

The stopping boundary values at each of the three interim analyses are shown in Table 4-1. Boundary information is reflected on two equivalent scales including hazard ratio and *P* value. As the error-spending (α) function is only utilized for the efficacy boundary, type I error spent at the efficacy interim and final analysis are shown in Table 4-1.

Table 4-2 Boundary Crossing Probabilities: Prior to Study Start

Analysis	Information Fraction	Events	Cumulative Boundary Crossing Probability			
			True HR = 1.0 (under H_0)		True HR = 0.8 (under H_1)	
			Efficacy	Futility	Efficacy	Futility
1	0.3	301	0	0.49	0	0.025
2	0.5	502	0	0.735	0	0.04
3	0.7	703	0.000083	NA	0.21	0
4	1.0	1004	0.022	0.978	0.919	0.081

HR = Hazard ratio, H_0 = null hypothesis, H_1 = alternative hypothesis

Table 4-2 shows the cumulative probability of meeting the futility threshold assuming the true underlying hazard ratios are 1 and 0.8. The cumulative probability of declaring futility at either the 1st or 2nd interim analysis is 0.735 under the null hypothesis and 0.04 under the alternative hypothesis. The cumulative probability of stopping for efficacy at the 3rd or 4th analysis given a non-futile result at the 1st or 2nd interim look is 0.919 under the alternative and 0.022 under the null.

The boundaries are defined in EAST 6.4 to preserve Type I error at 2.5% under the assumption of a non-binding futility rule.

Overview of the IDMC Review Process:

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

Treatment group comparison will be evaluated based on the point and CI estimates of the hazard ratio and 1-sided Wald *P* value obtained from a covariate-adjusted Cox proportional hazards regression model including fixed effects for treatment, index MI type, index MI management, region, age (as a continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and management.

In the event the efficacy stopping boundary is crossed at the third interim analysis, the IDMC will also review treatment differences for key secondary endpoints, CV death, and subgroups. Prior to recommending early termination of the study due to efficacy, the IDMC will ensure the presence of positive trends for key secondary endpoints and consistency across subgroups for the primary MACE endpoint. In order to recommend early stopping for efficacy, a statistically significant benefit for CV death through 90 days must also be observed using at a two-sided 0.05 significance level. In considering both efficacy and safety data, an extremely compelling benefit/risk must be observed in order to recommend early stopping for efficacy.

If a decision is reached by CSLB and the Executive Committee to terminate the study early for efficacy, a final analysis will be conducted by CSLB to account for all confirmed events accrued during the conduct of the interim analysis.

4.6.1.2 Analysis of Safety Data

The IDMC will review accumulating safety data on an ongoing basis. In addition, the IDMC will evaluate the potential impact of CSL112 on hepatic, renal functions and immunogenicity at pre-specified time points.

Ongoing Safety Review:

Commensurate with its mandate to review ongoing safety data, the IDMC will monitor unblinded, confirmed MACE, all-cause mortality, heart failure as well as other safety data with the objective of ensuring the safety of study participants; the review frequency will depend on the recruitment and event accrual rates. Upon review of the safety data, the IDMC may recommend stopping the study due to significant safety issues or propose modifications to the study protocol.

Beginning at the time of the 30% interim analysis, the independent statistician will perform and IDMC will review result of statistical testing for all-cause mortality. A two-sided Wald *P* value significant at the 0.01 level in a direction favoring placebo will serve as a threshold for recommending study termination due to safety concerns. The Wald *P* value will be obtained from a covariate-adjusted Cox regression model including fixed effects for treatment, index MI type, index MI management, region, age (continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and management. Prior to a decision whether to recommend study termination, the

IDMC will conduct a further data review of subgroups and endpoints other than all-cause mortality.

Hepatic and Renal Function and Immunogenicity Review:

Central laboratory data for ALT, total bilirubin (TBili), and serum creatinine will be examined to evaluate the non-inferiority comparison of CSL112 relative to placebo when approximately 20% of subjects have completed visit 6 (Day 29).

Evaluation of hepatic function will be based on a demonstration of non-inferiority of CSL112 to placebo in the incidence rate of elevations in ALT (>3 x ULN) at any time up to Day 29. The placebo event rate of 2.7% is taken from the Phase 2b study AEGIS-I. A non-inferiority margin similar in magnitude to the background event rate is considered to be a clinically meaningful criterion and thus, the margin is set at 3%. The treatment difference in the incidence rates will be estimated along with a two-sided 95% CI using the Newcombe-Wilson method [Newcombe, 1998]. If the upper limit of the CI is less than the pre-specified non-inferiority margin of 3%, the effect of CSL112 on the liver will be considered to be non-inferior to placebo. In addition to the evaluation of the non-inferiority analysis, the IDMC will review AEs that may be related to hepatic dysfunction (right upper quadrant pain, anorexia, generalized pruritus, jaundice, and encephalopathy). The IDMC, using their clinical judgment and the outcome of non-inferiority evaluation, may recommend discontinuation of central laboratory sampling before infusions 2 and 3 in the remaining subjects.

The renal function assessment will be based on acute kidney injury (AKI), defined as a change from baseline (pre-infusion 1) in serum creatinine ≥0.3 mg/dL. The background rate of AKI is derived as a weighted average of the observed placebo event rate (3.9%) from AEGIS-I in subjects with normal renal function or mild renal impairment (RI) and the renal event rate [Tsai, 2014] for subjects with moderate RI (~10%) and either STEMI or NSTEMI. Assuming that 75% of randomized subjects in the current study will have normal renal function or mild RI, and 25% will have moderate RI, the background event is estimated to be 5.4% [0.75*3.9 + 0.25*10]. A non-inferiority margin similar to the background rate is considered to be a clinically meaningful criterion for the comparison of CSL112 to placebo. The treatment difference in the incidence rates along with a two-sided 95% CI [Newcombe, 1998] will be estimated. The upper limit of the CI will be compared to the pre-defined non-inferiority margin of 5%. The renal impact of CSL112 will be considered to be non-inferior to placebo if the upper limit of the CI is less than 5%. The IDMC has the discretion to

recommend discontinuation of laboratory samples prior to infusions 2 and 3 in remaining subjects.

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

For the subgroup with moderate renal impairment and a time delay between administration of contrast and IP that is < 24 hours, the IDMC will review data after each 20 subjects are enrolled in this subgroup and reach day 29 in order to assess for any possible effect of the IP on renal function. The reviews of this individual subgroup will continue until the IDMC determine they are no longer necessary. For the subgroups with a time delay between contrast administration and administration of IP of <48 hours (<24 hours and 24 to <48 hours groups), reviews by the IDMC chair, the statistician, and the nephrologist will be triggered when 50, 75, 300, and 400 subjects achieve Day 29 follow-up; reviews by the full IDMC will be triggered when 200 and 500 subjects dosed achieve Day 29 follow-up.

The non-inferiority assessment will serve as a minimum criterion for a potential IDMC decision to discontinue routine assessments of renal function prior to infusions 2 and 3. Prior to a decision to discontinue routine assessments of renal function at infusions 2 and 3, the IDMC will also utilize clinical judgment, considering the summary of results for the subgroups outlined above. The IDMC will also use clinical criteria and will review adverse events (AEs) that are related to acute kidney injury, defined as AEs with a MedDRA

Preferred Term included in the Acute Renal Failure narrow Standardized MedDRA Query (SMQ). Prior to any decision, the IDMC will also apply medical judgment to assess severity, reversibility and a change to the benefit-risk balance. After this planned interim renal evaluation, the IDMC will have the option to recommend discontinuing or continuing renal assessments prior to infusions 2 and 3 in the overall study population or in certain subgroups of either renal function (such as moderate renal impairment) or time interval between contrast administration and administration of IP. For example, if data are insufficient in a certain subgroup, the recommendation can be appropriately tailored to ensure adequate safety monitoring in all subgroups of subjects.

Blood samples drawn from the first 600 subjects (approximately 300 CSL112 and 300 placebo) or in the event of a serious hypersensitivity reaction or any event of angioedema will be assayed to detect the presence of binding antibodies to CSL112 and apoA-I. Samples from 300 subjects who receive CSL112 will provide a 95% probability of observing at least 1 positive immunogenicity result if the underlying rate is 1/100 (ie, 1%). The number (%) of subjects with positive results will be presented. The IDMC may request that additional samples be assayed if warranted by the results.

4.6.2 Interim Sample Size Re-estimation

MACE rates will be monitored by CSLB and the Executive Committee, using blinded data, to reach a decision on the final sample size prior to completion of the enrollment phase. The observed blinded event rate will be based on a 90-day Kaplan-Meier estimate using a time-to-event approach with appropriate censoring to account for unobserved data. If the observed blinded event rate is higher than expected, then fewer subjects than 17,400 may be enrolled, with a minimum of approximately 15,000 subjects, corresponding to a placebo 90-day event rate of 7.4%. Conversely, if the observed, blinded event rate is less than expected, more subjects may be enrolled, but the increase would be capped at approximately 20,600 subjects, corresponding to a placebo 90-day event rate of 5.4%. The decision regarding sample size adjustment will be made when approximately 75% of subjects have been enrolled or approximately 75% of events have been accrued, whichever occurs first, with communication to sites occurring approximately 3 months prior to close of enrollment. The actual number of subjects to be enrolled, within the pre-specified range (15000 to 20600), will be determined by the Executive Committee and sponsor and chosen to provide a total of approximately 1004 events for the primary outcome. A subgroup analysis will be performed at the time of

final reporting to assess the consistency of primary MACE results for cohorts enrolled before and after the site communication on sample size re-estimation.

The table below illustrates the sample size associated with hypothetical placebo 90-day event rates assuming a 20% risk reduction attributable to CSL112. Since the sample size re-estimation will be performed using blinded data, the observed event rate will be compared to the pooled event rate shown in Table 4-3 below.

Table 4-3 Event Rate for Re-estimating Sample Size

Event Rate (%)			Sample Size
Placebo	CSL112	Pooled	
7.40	5.92	6.66	15,000
6.40	5.12	5.76	17,400
5.40	4.32	4.86	20,600

5 Changes in the Conduct of Protocol Planned Analyses

Not applicable

6 Study Analysis Sets

6.1 Screened Analysis Set

The screened Analysis Set consists of all subjects who provide written informed consent.

6.2 Randomized Analysis Set

The Randomized Analysis Set is comprised of all subjects in the Screened Analysis Set who were randomized. Any subject who provides written informed consent and is assigned a treatment randomization number will be considered to have been randomized. This Analysis Set will be used to describe the disposition of study participants enrolled in the study.

6.3 Intent-to-Treat Analysis Set

The ITT Analysis Set is comprised of all subjects in the Randomized Analysis Set with the exception of subjects enrolled at site(s) excluded from analysis due to potential study misconduct. The ITT Analysis Set will utilize the treatment to which the subject was randomized regardless of the treatment actually received. This Analysis Set will be used to describe the study population and in the analyses of efficacy endpoints.

6.4 Modified Intent-to-Treat Analysis Set

The modified Intent-to-treat (mITT) Analysis Set is comprised of all subjects in the ITT Analysis Set who receive any amount of investigational product. The mITT Analysis Set will be analyzed using the treatment to which the subject was randomized, regardless of the treatment actually received.

6.5 Safety Analysis Set

The Safety Analysis Set is comprised of all subjects in the ITT Analysis Set who receive any amount of the investigational product, and will be analyzed based on the actual treatment received. The safety Analysis Set will be the primary population for summarizing and reporting safety data.

6.6 PK Analysis Set

The PK Analysis Set will comprise all subjects in the safety Analysis Set who consent to participate in the PK sub-study and have one or more post baseline measurable (>0) plasma concentration of apoA-I or PC. For analyses and displays based on the PK population, subjects will be classified according to treatment received regardless of the treatment group to which they were randomized.

6.7 PD Analysis Set

The PD Analysis Set will comprise all subjects in the Safety Analysis Set who consent to participate in the PD sub-study and have one or more post-baseline measurable (>0) concentration for cholesterol efflux parameters. Subjects will be classified according to treatment received regardless of the treatment group to which they were randomized.

7 General Considerations

Analysis datasets will be created according to Clinical Data Interchange Standards Consortium, and data will be displayed according to reporting standards defined in this SAP and output (tables, listings, and figures) formats.

SAS version 9.3 or higher will be used to perform all data analyses and to generate tables, figures, and listings.

Continuous variables will be summarized in terms of the number of observations (n), mean, standard deviation (SD), median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), minimum and maximum. Other descriptive statistics (eg, geometric mean, coefficient of variation) may be reported when appropriate.

Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will be identified with the analysis in the applicable SAP section.

Summary statistics of central tendency will be reported to one more decimal place than the collected data. Summary statistics of variability will be reported to one more decimal place than the commensurate measure of central tendency. For example, the mean and median for age will be reported to one decimal place because it is collected in full years. The standard deviation of age will then be reported to 2 decimal places. Descriptive percentages will be displayed to one decimal place. Displays of proportions will include 3 decimal places. Durations (in days) for adverse events will be displayed to the nearest integer.

Formatting for dates and times will be:

Dates only – ddmmmyyyy

Times only – hh:mm

Dates and times – ddmmmyyyy hh:mm

In general, for by-visit summaries, data recorded will be presented by nominal visit. Unscheduled assessments will not be included in by-visit summaries but will contribute to determination of Last Observed Value or End of Study Value. Unscheduled assessments will be included in data listings as well as the determination of best and worst case values.

All listings will be presented by treatment group and will include subject number.

Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.

Deviations from the analyses in this SAP will be identified in the clinical study report.

7.1 COVID-19 Impact

During the course of this study, the global COVID-19 pandemic occurred, impacting the study in a variety of ways. This section describes how the impact of COVID-19 will be reported.

Subject Disposition: Study Treatment Discontinuation or Study Discontinuation

If IP or study discontinuation is due to "subject decision", "withdrawal by subject", "physician decision", or "other' reason, then additional free text to indicate the relationship to COVID-19 will be captured on the IP disposition and study conclusion eCRF forms. The associated free text entry will include character string(s) related to "COVID-19" to allow identification of subjects discontinuing due to the pandemic.

If the reason for IP/study discontinuation is a non-fatal AE or death or an endpoint event that was negatively adjudicated, then the identifier of the specific AE resulting in discontinuation will be captured. Discontinuations due to COVID-19 will then be identified based on whether the corresponding preferred term is included in the COVID-19 standard MedDRA query (SMQ) narrow.

Cases of study treatment discontinuation or study discontinuation due to COVID-19 will be included in the summary of subject disposition.

Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by COVID-19 period, ie before and after pandemic onset. This will allow an assessment of whether subject characteristics changed after pandemic onset. For purposes of these summaries, COVID-19 pandemic onset will be considered to be 11 March 2020 which corresponds to the pandemic declaration date by the World Health Organization (WHO).

Subjects with enrollment date on or after the pandemic onset will be flagged in the listings of demographic and baseline characteristics.

Adverse Events

Adverse events associated with COVID-19, which can include a clinically significant laboratory finding like a positive test result for COVID-19, will be reported by investigators

following requirements outlined in the protocol. COVID-19 associated adverse events will be identified via MedDRA coding based on COVID-19 standard MedDRA query (SMQ) narrow. All COVID-19 associated adverse events will be included in standard AE tables.

Treatment-emergent adverse events (TEAEs) are defined as adverse events occurring on or after the study treatment start date. A summary table providing an overview of COVID-19 associated TEAEs will be generated to include the number and percentages of subjects as well as the number of events in each of the following categories:

- Any TEAE through day 90
- Any TEAE through end of study
- TEAEs related to study treatment
- TEAE leading to infusion interruptions
- TEAE leading to permanent discontinuation of study treatment
- TEAE leading to study withdrawal
- Serious TEAEs
- Fatal TEAEs
- Fatal TEAEs related to study treatment

A listing showing all COVID-19 associated adverse events will be provided.

COVID-19 vaccine data collection

Sites will be prompted to inquire if subject has received a COVID-19 vaccination prior to or during study participation and to record each dose of the vaccine on the concomitant medications form along with the exact date of administration and manufacturer of the vaccine. Standardized Drug Grouping (SDG) from WHO Drug Dictionary will be utilized to identify COVID-19 vaccines. Any vaccination related adverse events experienced by study participants after informed consent will be recorded on the AE/SAE eCRF page.

The data are planned to be summarized as described below:

- Summary table by SoC and PT of all AEs occurring within 7 days after COVID-19 vaccine administration
- Listing of all AEs occurring within 7 days after COVID-19 vaccine administration
- Listing of all subjects receiving COVID-19 vaccine

Visit Modality, Missed Visits and Missing Assessments

The eCRF "Visit" page allows different options for visit modality (direct and indirect contact), as well as whether a visit is missed. The protocol requires in-person contact at all visits except at visits 7 and 10 when phone contact with subject is permissible. When a visit modality that deviates from the protocol is reported by investigator, an edit check is triggered in RAVE requesting the site to provide an explanation for the deviation. Site response to the query will be searched for character strings related to COVID-19 and if so identified, will be retained as alternate visit modality due to COVID-19 and merged with eCRF data by subject ID and visit. Since assessments (eg, vital signs, laboratory data) to be collected at each visit are known, the data missing due to COVID-19 can be determined using the approach described above.

Assessments that were missed or required alternate visit modality (eg, telephone with subject or indirect contact with family member or care taker) due to COVID-19 will be summarized. In addition, number of subjects with missed visits or alternate visit modality, by visit, will be summarized. A listing of visit modality by subject and visit will be provided.

Primary Efficacy Endpoint

A supplemental analysis of the primary endpoint will be undertaken to assess the impact of COVID-19 on the primary objective utilizing the estimand [ICH E9 (R1)] defined below. For subjects with a missed dose or treatment discontinuation due to COVID-19 impact, censoring will be applied 7 days after last infusion received on schedule. Subjects receiving no infusions due to COVID-19 impact will be censored at the time of randomization. In the context of this estimand, COVID-19 impact can be either COVID-19 infection or logistical constraints due to COVID-19. Analysis will use the same proportional hazards regression model as for the primary analysis.

Estimand

COVID-19 Estimand is defined as the hazard ratio for CSL112 vs. placebo, allowing for non-initiation, missed dose or discontinuation of treatment due to non-COVID reasons, in addition to standard of care as taken, for time to first occurrence of CV death, MI or stroke through 90 days in subjects with ACS presenting with STEMI or NSTEMI and MVD, while patients have not died due to non-CV causes.

Overview of COVID-19 Impact

Number and percentages of subjects experiencing at least one of the following outcomes due to COVID-19 will be summarized in an overview table:

- Subjects with Any COVID-19 Impact
- Missing one or more assessments
- Missing Visit
- Alternate Visit Modality
- Study Treatment Discontinuation
- Study Discontinuation
- Any TEAEs
- Any Serious TEAEs
- Fatal TEAEs
- Receipt of COVID vaccine

7.2 Multicenter Studies

Treatment assignment is planned to be stratified by region including North America, Latin America, Western Europe, Central and Eastern Europe, and Asia Pacific. Sites will be grouped according to region. A summary table of recruitment by region, country, and site will be produced. Statistical analysis of efficacy endpoints will be adjusted for region.

Summary tables, figures, and listings will not be reported by investigator site nor will investigator site be a factor in any statistical models.

7.3 Treatment Descriptors

The following convention will be used to represent treatment groups in all displays:

Table 7-1 Description of Treatment Groups

Treatment Group		Data Display	Order of Treatment Groups
Code	Description		
A	CSL112	CSL112 6g	1
B	Placebo	Placebo	2

A Total column will be displayed on select displays (such as study population tables) and will be indicated in the table mock-ups. Display columns will be in group order, that is, the left-most treatment column will be Group 1 (CSL112 6g), followed by Group 2 (Placebo), followed by a Total column for selected displays as indicated in the display mock-ups.

7.4 Multiple Comparisons and Multiplicity

There are two possible sources of multiplicity in this study: one, the planned interim analysis for efficacy; two, the inclusion of three key secondary endpoints along with the primary endpoint in the formal hypothesis testing framework.

Inflation in type I error due to interim efficacy (ie, early termination for benefit) analysis will be controlled with the use of an alpha-spending function from the Rho family, as described in Section 4.6.

Issues related to multiplicity arising from testing the primary endpoint and key secondary endpoints will be addressed using the serial gatekeeping procedure [Dmitrienko et al, 2013] to control the overall experiment-wise error rate at a 1-sided 0.025 level. Three families of null hypotheses will be defined with family 1 consisting of the primary endpoint (ie, H_{01}), family 2 consisting of the 2 key secondary endpoints (H_{02} and H_{03}) and family 3 consisting of the third key secondary endpoint. The null hypothesis associated with each of these endpoints is given below:

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

If H_{01} is rejected at the interim analysis (ie, 1-sided $p < 0.000083$) or at the final analysis, then the hypothesis tests associated with the second family will be performed using the Hochberg procedure at a 1-sided, 0.025 type I error level. The testing will proceed from the

largest to smallest raw *P* value (step-up). The largest *P* value will be compared to a 0.025 significance level and if significant, the remaining null hypothesis will also be rejected; if not, the second *P* value will be compared to a 1-sided 0.0125 significance level. Testing will proceed to family 3 (H_{04}) at a 1-sided 0.025 level only if both family 2 null hypotheses, H_{02} and H_{03}, are rejected.

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

8 Data Handling Conventions

Treatment assignments will be applied to clinical data at the time of the database lock. The randomization schedule and clinical data will be merged by randomization number thus matching subjects to the correct treatment assignment.

8.1 Missing Data

8.1.1 Missing Baseline Covariates

Missing values for baseline risk factors including diabetes mellitus, peripheral artery disease (PAD), or prior MI can be expected to occur in a small subset of subjects enrolled in the study. These risk factors are included in the proportional hazards regression model for the analysis of the primary and other endpoints as independent covariates. To prevent the casewise deletion of records due to missing baseline covariates, a single imputation from the Fully Conditional Specification (FCS) under a generalized logit distribution (appropriate for non-ordered categorical data) and missing at random assumption will be obtained [White et al, 2011]. The imputation model will include all the covariates considered in the analysis of the primary endpoint but not the treatment or outcome. The inclusion of a term for interaction between index MI type and management type will be omitted if cells with zero events are encountered as it could result in failure to fit the model. The completed dataset will be saved and utilized for all planned analyses as applicable. The SAS code fragment is shown in Appendix 15.5.

8.1.2 Imputation of Non-Date Missing Data

As per the protocol, subjects are to be followed for 365 days regardless of compliance with treatment or protocol; however missing efficacy event data can occur if a subject withdraws

consent for additional post-discontinuation assessments. Imputation of missing event data when subjects are non-administratively censored is described in Section 10.1.1.

If the investigator assessment of causal relationship to study treatment for adverse events (AEs) and serious adverse events (SAEs) is missing then the adverse events will be assumed to be “related”. There will be no other imputation for missing data other than as described in Section 8.1.3 for partial dates and times.

8.1.3 Imputation of Partial Dates

Partial dates will be imputed dates for the purpose of slotting medications, adverse events, and other data into distinct study periods as well as for sorting in data listings. They will not be used to derive study day, duration (eg, duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date for time to event variables.

Partial date imputation will follow Analysis Data Model (ADaM) conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

Blank: indicates that no imputation was done

D = 'Day': indicates that the day portion of the date is imputed

M = 'Month': indicates that the month and day portions of the date are imputed

Y = 'Year': indicates that the entire date (year, month, and day) is imputed

Algorithms for imputing partial dates for AE and concomitant medications are given below.

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. They will not be used to calculate duration of AEs. If an AE start or end date is missing, then the duration of the AE will be set to missing.

Adverse Events

Date	Missing Element	Rule
Start Date	day, month, and year	• Do not impute completely missing AE start dates • The AE will be deemed treatment-emergent if the AE end date does not indicate that the AE ended prior to study treatment start date

	day, month only	• If the study treatment start date is not missing:
		  • If the year of AE start date is the same as the year of study treatment start date
		  ▪ If the AE end date indicates the AE ended prior to study treatment start date then set AE month and day to January 1
		  ▪ Otherwise set month and day of AE start date to study treatment start date
		• If the study treatment start date is missing then set month and day of AE start date to January 1.

	day only	• If the study treatment start date is not missing:
		  • If the month and year of AE start date is the same as the month and year of study treatment start date
		  ▪ If the AE end date indicates the AE ended prior to study treatment start date then set day of AE start date to the 1st of the month
		  ▪ Otherwise set day of AE start date to study treatment start date
		▪ If the study treatment start date is missing then set day of AE start date to 1st day of the month of AE start date.

End Date	any date element	No imputation for completely or partially missing AE end dates; as applicable, report the AE as ongoing and the AE duration as missing.

Concomitant Medications

Medication start and end dates will be imputed as necessary to define the time period of usage through study Day 90 or the end of study. Imputed dates will be recorded in the concomitant medications analysis dataset with a flag variable as previously described to indicate the imputed portion(s) of date.

Concomitant Medications

Date	Missing Element	Rule
Start Date	day, month, and year	Completely missing medication start dates will not be imputed and all values that depend on this date will be set to missing • Concomitant medication if medication end date is on or after treatment start date
	day, month	• If study treatment start date is missing or medication end date is before treatment start date then day and month portion of the medication start date = January 1. • If study treatment start date is not missing & medication end date is on or after treatment start date then medication start date = treatment start date
	day	• If study treatment start date is not missing: ➢ If the month and year of the medication start date is the same as the month and year of treatment start date then ▪ If the medication end date indicates the medication ended prior to the study treatment start date then set the day portion of medication start date to the 1st of the month ▪ Otherwise set the day of the medication start date to the day of the study treatment start date • Otherwise set day of medication start date to the 1st of the month
End Date	day, month, and year	Completely missing concomitant medication end dates will not be imputed; all values that depend on this date will be set to missing • The medication will be deemed to be concomitant and ongoing
	day, month	If the medication partial end date contains the year only, then set medication end date to the earliest of [December 31 or the date of the last safety assessment or death up to day 90 in the study].
	day	If the partial medication end date contains month and year, then set the day of the medication end date to the earliest of the last day of the end month reported, the last safety assessment completed or the date of death up to day 90 in the study]

8.2 Derived Variables

The following sections provide a general description of the derived variables for data analyses. Separate analysis dataset specifications provide full details on all data derivations and transformations.

8.2.1 Reference Dates

There are two reference dates defined in this study:

- The efficacy reference date is the date of randomization and will be used to calculate study day as well as time to event for efficacy measures
- The safety reference date is the treatment start date, and will be used to calculate study day for safety measures.

8.2.2 Study Day for Safety Measures

If the date of interest occurs on or after the safety reference date then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs before the safety reference date then the safety study day will be calculated as (date of interest – safety reference date). There is no safety study day 0.

8.2.3 Study Day for Efficacy

If the date of interest occurs on or after the efficacy reference date then efficacy study day will be calculated as (date of interest - efficacy reference date) + 1. If the date of interest occurs prior to the efficacy reference date then efficacy study day will be calculated as (date of interest – efficacy reference date). There is no efficacy study day 0.

8.2.4 Durations

Durations of events (eg, duration of an AE or medication) calculated in days will use only dates based on the algorithm given below:

- (End date – Start date) + 1

Durations calculated in hours (h), such as duration of infusion, will be calculated using date/time variables shown below:

- (End date/time – Start date/time)

Where durations calculated in days have to be reported in months or years, the following approach will be taken:

Months = days / 30.4375

Years = days / 365.25

8.2.5 Baseline Definition

Baseline is defined as the most recent, non-missing value prior to the date of first infusion of study treatment. For subjects who do not receive study treatment during the study, baseline is defined as the latest, non-missing collected value on or before Visit 2. Subjects without such a result will be considered as missing the baseline value.

8.2.6 Change from Baseline

Change from baseline will only be calculated for measures that have post-baseline records. Change from baseline is calculated as:

(Visit value) – Baseline value.

Percentage change from baseline is calculated as:

((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and percentage change from baseline is set to missing as well.

8.2.7 Multiple Assessments

All data will be reported to according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). All other unscheduled data will be included in worst case post-baseline summaries.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

8.2.8 Actual Treatment

The subjects' actual treatment will be derived from exposure data. Kit ID dispensed by the IRT and actual kit ID used will be recorded. If a subject's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment. If a subject receives a study treatment that is different from the assigned treatment, then the following rule will apply: the actual treatment group will be set to CSL112 if at least one infusion of CSL112 is administered regardless of randomized treatment; if a subject assigned to CSL112 receives only infusions of placebo then the actual treatment will be defined as placebo.

8.2.9 Derivation Algorithms

Derivation of BMI

BMI will be calculated using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (m)}]^2$$

The height and weight measured at Screening will be used (if available).

Derivation of Hospitalizations for coronary, cerebral, or peripheral ischemia:

- Total number of hospitalizations per subject will be derived by defining a cumulative count variable that is incremented with each new date of positively-adjudicated hospitalization. The analysis dataset will include one record per subject, with a count variable containing the total number of hospitalizations.

Derivation of Indirect bilirubin:

The calculation of indirect bilirubin is applicable when both TBili and direct bilirubin are reported by the central laboratory.

- Indirect bilirubin (µmol/L) = TBili (µmol/L) – direct bilirubin (µmol/L)

Derivation of Estimated Glomerular Filtration Rate (eGFR):

For the purpose of safety analyses, the eGFR value will be calculated for both local and central laboratory reported results. The CKD-EPI equations shown in Table 8-1 will be used:

Table 8-1 CKD-EPI Equations

Race and Sex	Serum Creatinine (mg/dL (µmol/L)	Equation
Black		
Female	≤ 0.7 (≤ 62)	$eGFR = 166 * (Scr/0.7)^{-0.329} * 0.993^{age}$
	> 0.7 (> 62)	$eGFR = 166 * (Scr/0.7)^{-1.209} * 0.993^{age}$
Male	≤ 0.9 (≤ 80)	$eGFR = 163 * (Scr/0.9)^{-0.411} * 0.993^{age}$
	> 0.9 (> 80)	$eGFR = 163 * (Scr/0.9)^{-1.209} * 0.993^{age}$
White or Other		
Female	≤ 0.7 (≤ 62)	$eGFR = 144 * (Scr/0.7)^{-0.329} * 0.993^{age}$
	> 0.7 (> 62)	$eGFR = 144 * (Scr/0.7)^{-1.209} * 0.993^{age}$
Male	≤ 0.9 (≤ 80)	$eGFR = 141 * (Scr/0.9)^{-0.411} * 0.993^{age}$
	> 0.9 (> 80)	$eGFR = 141 * (Scr/0.9)^{-1.209} * 0.993^{age}$

The CKD-EPI equation can be expressed in a single equation as:

- $eGFR\ (derived) = 141*\min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] x 1.159 [if black]

Where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. In Table 8-1, the multiplication factors for race and sex are incorporated into the intercept, which results in the different intercepts for race and sex combinations.

Stratification and Prognostic Factors

The stratification variables, demographic characteristics, baseline risk factors and/or prognostic variables, and variables indicating compliance with evidence-based therapy will be added to the dataset at a minimum to describe the study population, and to support analyses of efficacy data and subgroups: The code descriptions will be used as the labels for each subgroup level. When performing analyses using stratification factors, the original data used for randomization will serve as the primary source. A sensitivity analysis may be performed if there is a substantial difference between the strata used for randomization and corrected strata. Distinct naming conventions will be used such that identification of the source of stratification factors will be straightforward.

The variables defined below include the study treatment to which subjects are randomized as well as the factors used for stratifying the randomization. These variables will be included in the ADaM datasets to support analysis. In addition, some of the variables listed will be included in the subgroup analysis of the primary endpoint. For such variables, the group coded as 0 will serve as the reference group for statistical comparisons. In other words, if the estimated hazard ratio is less than 1 it will be interpreted as favoring the non-reference group relative to the reference group.

Randomization Variables:

Treatment:

1 = CSL112
0 = Placebo

Index MI Type:

1 = STEMI
0 = NSTEMI

Management of Index MI:

1 = Managed with PCI
0 = Managed medically

Region (1):

1 = North America
2 = Latin America
3 = Western Europe
4 = Central and Eastern Europe
0 = Asia Pacific

Demographic Characteristics:

Gender:

1 = Female
0 = Male

Age at baseline categorized as follows:

1 = Less than 65 years old
0 = Greater than or equal to 65 years old

Race categorized as:

3 = Other/multiracial (includes Native American, Pacific Islander, Multiracial, & other)
2 = Asian
1 = Black/African-American
0 = White

Ethnicity categorized as:

1 = Hispanic
0 = Non-Hispanic

Region (2):

1 = North America (U.S. and Canada)
0 = Rest of World (RoW)

Baseline Risk Factors

Meet modified enrichment criteria (diabetes on pharmacotherapy or at least two of age ≥ 65 years, PAD, history of prior MI (excluding index MI):

1 = Yes
0 = No

Planned Staged PCI:

1 = Yes
0 = No

Diabetes Mellitus on Pharmacotherapy:

1 = Yes
0 = No

Prior Myocardial Infarction (MI) [excluding index MI]:

1 = Yes
0 = No

Prior PCI [excluding index MI]:

1 = Yes
0 = No

Peripheral Artery Disease:

1 = Yes

0 = No

Renal Function (based on calculated eGFR measurement as given in Table 8-1)

0 = Normal renal function: ≥ 90 mL/min/1.73 m2

1 = Mild renal impairment: ≥ 60 - <90 mL/min/1.73 m2

2 = Moderate renal impairment: ≥ 30 - <60 mL/min/1.73 m2

HDL (mg/dL):

1 = Low: <1.04 µmol/L/40 mg/dL for men and <1.3 µmol/L/50 mg/dL for women

0 = Normal: ≥1.04 µmol/L/40 mg/dL for men and ≥1.3 µmol/L/50 mg/dL for women

Medication usage at the time of Index MI:

Thrombolytic use:

1 = Yes

0 = No

Medication usage at the time of randomization:

Aspirin use:

1 = Yes

0 = No

PCSK9 Inhibitor use:

1 = Yes

0 = No

P2Y12 Anti-platelets use:

1 = Yes

0 = No

Dual anti-platelet therapy (aspirin and P2Y12)

1 = Yes

0 = No

Statin use:

0 = None
1 = High Intensity
2 = Moderate Intensity
3 = Low Intensity

Beta-blockers

1 = Yes
0 = No

Non-statin lipid modifying agents (including niacin and fibrates):

1 = Yes
0 = No

Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin II Receptor Blockers (ARB):

1 = Yes
0 = No

SGLT2 Inhibitor:

1 = Yes
0 = No

8.3 Study Periods Relative to Treatment

8.3.1 Time in Relation to Treatment

Adverse events, serious adverse events, death, laboratory data, vital signs will be assigned to the study time periods defined below. Partial dates will be imputed into full dates for AE start date and concomitant medication start and end dates, (see Section 8.1.3) for assigning data to the appropriate study periods.

Pre-therapy is defined as the time prior to the first dose of study treatment.

On-therapy is defined as the time from the start of first infusion to one week following the end of the last infusion of study treatment.

Post-therapy is defined as any time beyond the on-therapy period to completion of the study. The first dose day (Day 1) is considered to be on-therapy for adverse events and concomitant medications.

8.3.2 Study Time Periods for Medications

Prior ACS-related medications taken by subjects in the 4 weeks before screening will be captured in a targeted manner. All medications taken or administered at any time during the time from informed consent through Visit 8/Day 90 will be collected. Medications contributing to or used in the treatment of an SAE will be collected through the EoS. For the purpose of summarizing medications usage during the study, the following designation will be used: “Concomitant”, defined based on a 90-Day window and “Concomitant through End of Study”.

Designate as “Concomitant” if the medication *start* date is before study day 90 and any of the following conditions is met:

- If the medication *end* date is after the study treatment start date
- If the medication *end* date is missing
- If the study treatment start date is missing

Designate as Concomitant through End of Study” if the medication *start* date is before subject’s last contact date and any of the following conditions is met:

- If the medication *end* date is after the study treatment start date
- If the medication *end* date is missing
- If the study treatment start date is missing

Medication usage will be also categorized relative to first dose of investigational product as described below.

Start date relative to treatment

- Assigned to 'BEFORE' if the medication start date is prior to study treatment start date; or if subject has not taken any study treatment; or the medication start date is missing and the medication end date is before the study treatment start date.
- Assigned to 'DURING' if the medication start date falls into the on-therapy period as defined in Section 8.3.1 or the medication start date is missing.

- Assigned to 'AFTER' if the medication start date is after the on-therapy period defined in Section 8.3.1.

End relative to treatment

- Assigned to 'BEFORE' if the medication end date is prior to study treatment start date or if the subject has not taken any study treatment.
- Assigned to 'DURING' if the medication end date falls into the on-therapy period; or the medication end date is missing and the medication start date relative to treatment is not assigned to 'AFTER').
- Assigned to 'AFTER' if the medication end date is after the on-therapy period or the medication end date is missing and the medication start relative to treatment is assigned to AFTER'.

Baseline medications:

Any medication that started on or prior to the date of first infusion and the end date is either after the date of first infusion or missing (implying the medication is ongoing) is defined as a baseline medication.

8.4 Values of Potential Clinical Importance

8.4.1 Laboratory Parameters

A laboratory value that is outside the reference or the normal range can be categorized as either a high abnormal value (a value above the upper limit of the normal [ULN]) or low abnormal value (a value below the lower limit of the normal). A laboratory parameter can take on both high and low abnormal values at different Safety assessment visits. Note that a laboratory value outside the reference range is not necessarily one of potential clinical importance.

Specific laboratory values of potential clinical importance are those that exceed the thresholds defined below:

Absolute change from baseline in serum creatinine during the Active Treatment Period will be categorized based on SI units of µmol/L. Equivalent conventional units are shown for descriptive purposes:

≥ 27 µmol/L to ≤ 44 µmol/L (≥ 0.3 to ≤ 0.5 mg/dL)

> 44 µmol/L (> 0.5 mg/dL)

Increases in serum creatinine relative to baseline value:

≥ 1.5x baseline value

≥ 2.0x baseline value

≥ 3.0x baseline value

Raw serum creatinine value ≥ 354 µmol/L (4.0 mg/dL)

A decrease in eGFR ≥ 25% from baseline during the active treatment period

Changes in hepatic status occurring at any time during the study:

ALT > 3x ULN

ALT > 5x ULN

ALT > 10x ULN

Serum TBili† > 2x ULN

† Note that for subjects with a history of Gilbert's syndrome, serum bilirubin assessments will be based on direct bilirubin.

8.4.2 Vital Signs

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the predefined markedly abnormal criteria detailed in Table 8-2.

Table 8-2 Vital Signs Markedly Abnormal Criteria

Variable	Unit	Low	High
Systolic Blood Pressure	mmHg	≤ 90 AND a decrease from baseline ≥ 20	≥ 180 AND an increase from baseline ≥ 20
Diastolic Blood Pressure	mmHg	≤ 50 AND a decrease from baseline ≥ 15	≥ 105 AND an increase from baseline ≥ 15
Pulse	Bpm	≤ 50 AND a decrease from baseline ≥15	≥ 120 AND an increase from baseline ≥ 15
Weight	Kg	Percentage decrease from baseline ≥ 7.0 %	Percentage increase from baseline ≥ 7.0 %

9 Study Population

The disposition of subjects enrolled in the trial will be described based on the Screened and Randomized Analysis Sets. All other tables and listings in this section will be based on the ITT Analysis Set, and all summaries and data listings will use treatment labels as specified in Section 7.3. Summary tables will include columns for treatment groups and total.

9.1 Disposition of Subjects

The study is designed to conclude at least 365 days after the last subject is randomized.

Study visits are expected to be completed in person at all visits except visits 7 (Day 60) and 10 (Day 270) when visit completion by phone contact with subject is permitted. The investigator reports the type of contact at each visit, whether direct contact with subject (in-person or phone) or indirect based on contact with family member or care taker, or primary physician or medical record review, publicly available sources or other. A visit is considered to be complete if the type of contact is direct (in-person or phone) or with family member or care taker since it allows for full ascertainment of MACE. Otherwise, a visit will be considered to be incomplete.

The date of last MACE ascertainment will be derived for each subject and used in the analysis of time-to-event endpoints and count data. It is defined as the later of the last completed visit date or the date of the last positively adjudicated endpoint regardless of event

type. If a subject is missing both dates then the date of last MACE ascertainment will be set to the randomization date.

Subject disposition during the study will be summarized by treatment group and will include the information listed below:

Subject status:

- Number of subjects screened, number of screen failures, and number randomized
    - Of the number randomized, number of subjects receiving all four infusions, fewer than four infusions (discontinued and skipped dose) and no infusion
- Primary endpoint completion status - In order to be defined as a primary endpoint completer, one of the following conditions has to be met:
    - Ascertainment for MACE endpoint has been obtained through Study Day 90 or later or
    - Death prior to Study Day 90
    - Positively adjudicated primary composite MACE prior to Study Day 90
- Study completion status – In order to be defined as a study completer, one of the following conditions must be met:
    - The answer to the question “did the subject complete the last expected visit per study protocol?” at study conclusion is yes and direct contact with subject or indirect contact with family member or care taker is reported at Visit 11. Note: Assessment of study completion based either on medical records review, publicly available sources or any other method will not be considered as study completer in the analysis. The reason for discontinuation will be derived and displayed as due to indirect contact since full ascertainment of MACE cannot be considered as complete based on these methods of follow-up.
    - The answer to the question “did the subject complete the last expected visit per study protocol?” at study conclusion is no and reason for study withdrawal is reported as death in the eCRF.
- Reasons for study withdrawal will be presented in the order they are displayed in the eCRF with the following exceptions: study discontinuation due to death will not be reflected in this summary table as these subjects are considered to be completers in the analysis.

- Vital status will be summarized:
    - At Study Day 90
    - At study conclusion for subjects completing the study and
    - At Study Day 365 for subjects who discontinue from study participation prior to Study Day 365

  Categories of study disposition status include completer, withdrawal of consent by subject, lost to follow-up, protocol deviation, or other. Complete withdrawal of consent prohibits further follow-up, including for vital status, unless allowed by local regulations. In lieu of complete withdrawal of consent, subjects may agree to limited or alternate methods of follow-up.

  - In cases where only follow-up by medical record review is agreed to, the investigator will complete follow-up visits (according to the protocol defined visit schedule) based on medical record review to gather information on MACE outcomes. In such cases, investigator will report subject has completed participation in the study however the derived study conclusion will be 'no' and vital status at Study Day 365 of "Alive" will be derived.
  - In cases where only follow-up to ascertain vital status at Visit 11 is agreed to: investigator will report that subject did not complete the study due to "other" reason. The investigator will further record the date subject was confirmed to be alive or dead in a free text field on the study conclusion eCRF page. The study day of confirmed to be alive or dead relative to randomization date will be computed and if greater than 365, vital status will be set to Alive. If date confirmed to be alive is less than 365 then vital status at day 365 will be set to Unknown. If date confirmed to be dead is less than 365 then vital status at day 365 will be set to dead.
  - In case of complete withdrawal of consent, the date last known to be alive will be reported on the study conclusion eCRF page. A similar derivation as described in the previous paragraph will be applied to determine vital status at study day 365.

- Fraction of missing person years – the primary assessment of the extent of missing data will be based on the proportion of missing person years during the first 90 study days. For calculation of this proportion, subjects completing 90 days of follow-up or experiencing death prior to 90 days are assigned a score of 1 while subjects not completing 90 days of follow-up are assigned a score corresponding to the fraction of

the 90 day follow-up completed. The proportion of missing person years is defined as 1 – (sum(score)/n) where n is the total number of subjects.

A similar statistic will be presented to summarize the extent of missing person years through study day 365.

Analysis Sets:

- Number of subjects included in each of the analysis sets, described in Section 6, will be summarized as counts and percentages

Sub-populations:

- Subjects in each subpopulation as defined by randomization strata will be summarized. The strata information from the eCRF as well as from the IRT system will be presented separately

Enrolment:

- Number randomized will be summarized by region, country, and site

Subject completion by visit:

- Number (%) of subjects completing each planned study visit will be summarized along with the type of contact. Visit completion is defined as direct contact with study participant (in person visit or phone with subject) or indirect contact with family member/care taker.

The following listings of individual subject data will be provided:

- Reason for screen failure as collected in the eCRF
- The listing of subjects discontinuing study treatment including reason
- Reasons for study withdrawal including the date of discontinuation
- Subjects excluded from the Randomized, ITT, mITT, and Safety Analysis Sets

9.2 Protocol Deviations

A prospectively defined protocol deviation plan will be followed to identify instances of major deviations from the study protocol. In general, major protocol deviations are defined as those having a direct negative effect on the rights, safety, well-being of study subjects, or the integrity of the data for key conclusions related to efficacy or safety. Major protocol deviations will be grouped by type of deviations in the summary table. Within each type, number (%) of subjects with a specific deviation will be presented. In addition, listing(s) of individual subjects with major deviations will be generated.

9.3 Demographic and Baseline Characteristics

9.3.1 Demographic Characteristics

The following summaries will be provided by treatment group and based on the ITT Analysis Set:

- Demographic characteristics including age, sex, race, and ethnicity. Subjects may be included in more than one racial category if so reported in the eCRF. In addition to summarization as a continuous variable, age will also be categorized and frequencies will be presented for age categories ≥18-<65, ≥65-<74, ≥75-<85, and ≥85
- Distribution of subjects across region and country
- Demographic characteristics by region

9.3.2 Baseline characteristics

Baseline characteristics will be summarized as follows overall and by region based on the ITT Analysis Set:

- Height (cm), weight (kg), BMI (kg/m^2) will be summarized as appropriate to continuous variables
- Renal function based on eGFR values categorized as normal (eGFR ≥90 mL/min/1.73 m^2), mild impairment (eGFR ≥60-<90 mL/min/1.73 m^2), moderate impairment (eGFR ≥30-<60 mL/min/1.73 m^2), and severe impairment (eGFR<30 mL/min/1.73 m^2)
- Baseline HDL (µmol/L), LDL (µmol//L), cholesterol (µmol//L), and triglycerides (µmol/L) will be summarized as continuous variables
- Baseline HDL categorized as normal or low using gender-specific cut points
    - Male: < 1.04µmol/L (<40 mg/dL)
    - Female: <1.3 µmol/L (<50 mg/dL)

- Characteristics of Index MI at presenting hospital:
  - Number of angina events in the 24 hours prior to presentation
  - ECG with significant ST segment deviation (yes, no)
  - Killip Class (I, II)
  - Heart rate and blood pressure
- Characteristics of Index MI
  - Type (STEMI or NSTEMI)
  - Management type – PCI or medically managed
  - Whether or not coronary angiography is performed and if yes, present:
    - Receipt of prophylaxis for contrast-induced nephropathy
    - Prophylaxis type
  - Multivessel disease (MVD) assessment
  - Location of stenosis ≥50%
  - Identification of infarct-related artery
  - Medications of interest taken prior to the index MI and used to treat index MI
  - If percutaneous coronary revascularization is performed, type and location of treated vessel(s) will be presented
  - Left ventricular ejection fraction (LVEF) in those assessed

9.3.3 Targeted and Other Medical History

The following targeted medical history at screening will be summarized by treatment group and by region based on the ITT Analysis Set to describe the patient population enrolled in the study:

- Known coronary artery disease
- Prior MI excluding index MI
- Prior (excluding index MI) coronary revascularization performed and if yes, type of procedure
- Chronic kidney disease
- History of congestive heart failure within the past year
- Peripheral Artery Disease

- Moderate to severe valvular heart disease
- Atrial fibrillation
- Cerebrovascular disease and if yes:
    - Transient ischemic attack (TIA)
    - Ischemic stroke
    - Hemorrhagic stroke
    - Carotid endartectomy
    - Carotid stenting
- Hypertension
- Gilbert's syndrome
- Hypercholesterolemia or use of medication for hypercholesterolemia prior to index MI
- Diabetes mellitus – type and pharmacotherapy for diabetes will be summarized. In addition, diabetes mellitus on pharmacotherapy is defined as receipt of oral medication, insulin or other non-insulin injectable while diet therapy only or no treatment are considered as not meeting the criterion.
- Smoking or tobacco usage – current or former user
- e-cigarette usage – current or former

By subject listing of all medical history will be produced.

9.4 Prior and Concomitant Medications

The ITT Analysis Set will be used for describing medication usage during the study. Prior ACS-related medications taken by subjects in the 4 weeks before screening will be collected in a targeted manner. The number (%) of subjects receiving each medication of interest will be summarized.

Medication usage from the time of informed consent through 90 days from randomization will be captured. Medications intended to diagnose or treat SAEs will be captured through the end of study. All medications will be coded using the WHO Drug coding dictionary and summarized to show the number and percentage of subjects taking concomitant medications. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary. Medications will be grouped by ATC code and summarized in alphabetical order by generic

term within ATC code. Subjects with multiple instances of the same medication will be counted once in the summary table(s).

The following output will be generated:

- Summary of Concomitant Medications through 90 days
- Summary of Concomitant Medications through End of Study
- ACS-related concomitant Medications of Interest including:
  - Aspirin
  - P2Y12 anti-platelets
  - PCSK9 inhibitors (PCSK9i)
  - Beta-blockers
  - ACE-I or ARB
  - Statins will be categorized as high, moderate, or low intensity, and none
  - Non-statin lipid-modifying agents

The number (%) of subjects receiving aspirin, statins, and P2Y12 inhibitors will be presented at study days 90, 180, and 365 for ascertaining the degree of compliance with evidence-based therapy; reasons for not doing so will be summarized with number (%) of subjects presented for each medication and reason.

Identification of ACS-related Medications:

Concomitant medications will be categorized as belonging to one or more of predefined ACS-related drug classes of interest as follows: a comprehensive list of individual medications within each drug class of interest will be prospectively generated from the WHO drug dictionary, retaining the associated ATC level 4 code and preferred code for each medication. For statins, the list is also populated with dosages corresponding to low, moderate, or high intensity as defined by practice guidelines. This list will be merged with the coded concomitant medications usage data in the study database by ATC level 4 and preferred terms to identify matching records. The database will contain one record per subject and medication received when there is a match.

9.5 Prior and Concomitant Procedures

The number (%) of subjects undergoing a PCI for the index MI will be summarized based on the ITT Analysis Set. Additional coronary revascularizations planned at the time of index MI (ie, staged PCIs) will be summarized as occurring before or after randomization. Planned procedures which are performed after randomization and adjudicated by the CEC will be identified based on the procedure type and adjudication outcome (procedure type = PCI, procedure date is after randomization date, adjudication criteria are not met, or criteria are met and adjudicated as an elective, staged procedure). All coronary revascularization procedures occurring post-randomization will be adjudicated by the CEC. The number (%) of subjects undergoing coronary revascularization will be summarized as adjudicated through 90 days, and 365 days. This table will include the total number of procedures undergone by study subjects. In each period, the type of procedure as well as elective (staged, non-staged, or unplanned) or urgent nature of the procedure will be summarized. Procedures not reported by investigator but identified during back end review of study data and triggered for adjudication will be included.

All investigator-reported procedures for cerebral or peripheral ischemia reported on or after randomization through study Day 90, Day 91-180, and Day 181-365 will be summarized using the ITT Analysis Set and will present the number (%) of subjects undergoing a procedure by type and treatment group.

Supporting listing of individual subject data will be generated for prior and concomitant procedures.

The exploratory endpoint, select surgeries and procedures related to hospitalization for coronary, cerebral, or peripheral ischemia will consider all revascularization procedures occurring during a positively-adjudicated hospitalization for ischemia. This analysis will count procedures with dates contained within admission and discharge dates as reported by investigator or within 10 days following admission date if the discharge date is not available. Positive adjudication of triggered coronary revascularization procedures will also be included based on the CEC-reported procedure date.

Site-reported hospitalizations will be used in summarizing and analyzing endpoints related to medical resource utilization with the exception of select surgeries and procedures which is described above. Post-hospitalization discharge status will be presented for site-reported and positively adjudicated ischemic hospitalization events. Hospitalizations may be new or prolongation of an existing one. The index MI hospitalization extending past the date of

randomization will be excluded unless the extension is due to a treatment-emergent serious adverse event. Overlapping hospitalization dates will count as a single event with the longest duration utilized in analysis. A supporting listing of individual subject data will be provided.

9.6 Examination of Regions and Timing of First Infusion

Descriptive summaries of the following timings (hours) will be produced by treatment group and region based on the ITT Analysis Set.

- Onset of index MI symptoms to each milestone shown below will be summarized overall and by index MI type:
    - FMC
    - Angiography
    - Randomization
    - First infusion of investigational product
- FMC to start of angiography and end of angiography contrast administration
- FMC to randomization by angiography status and to first infusion
- End of angiography contrast to randomization and to first infusion
- Randomization to first infusion

In addition to the above summaries, time from angiography to start of first infusion will be presented in categories shown below. These data will also be included in a listing of individual subject data.

- <12 hours
- ≥12 hours - <24 hours
- ≥24 hours - <48 hours
- ≥48 hours - <72 hours
- ≥72 hours - <96 hours
- ≥96 hours - ≤120 hours
- >120 hours

10 Efficacy

This section describes the planned analyses of efficacy endpoints. The ITT Analysis Set will be the primary analysis set for all efficacy variables. See the CEC charter for complete definitions of MACE. The primary (or leading) analysis of each composite endpoint including MI will be performed including all MIs.

MACE ascertainment occurs from the time of randomization through Study Days 90, 180, 365, and end of study. Analysis of data from each time period will only include cardiovascular events occurring during that time period. As per the schedule of assessments, the conclusion of study participation is expected to occur between study day 365 and 379 from the time of randomization. Therefore, the end of study period is defined as the time from randomization through the date of study conclusion (even if the study day of conclusion exceeds 379). The analysis of efficacy endpoints through the end of study will include events beyond day 365 and through study conclusion. Cardiovascular endpoints reported and adjudicated after the study conclusion date will not be considered in any of the planned analyses and will instead be limited to a data listing.

10.1 Analysis of Primary Endpoint

The primary endpoint is defined as the time to first occurrence of any component of the composite MACE, ie, CV death, MI, or stroke, from the time of randomization through 90 days. This analysis will be based on events adjudicated and confirmed by the CEC. All adjudicated MIs from randomization through 90 days will be included in the analysis of the primary endpoint. A total of 1004 events for the primary composite endpoint are targeted as per the power calculation. However, the final analysis will include all events that are observed during the 90-day interval even if that number is larger or smaller than the target.

For each subject, time to event is defined as the time (number of days) from randomization to the first occurrence of confirmed CV death, MI, or stroke during 90 days of follow-up. For subjects without an event and last MACE ascertainment date occurring at least 90 days after randomization, an administrative censoring will be applied at 90 days. For subjects that experience a non-CV death prior to 90 days of follow-up, censoring will occur on the date of death. All other subjects will be censored on the last MACE ascertainment study day. The analysis of the primary endpoint will be based on positively adjudicated, CEC confirmed events occurring in the 90 days following randomization.

The estimand [ICH E9 (R1)], ie, the quantity to be estimated, in the primary analysis is defined as the hazard ratio for CSL112 vs. placebo, regardless of non-initiation, missed dose or discontinuation of treatment, in addition to standard of care as taken, for time to first occurrence of CV death, MI or stroke through 90 days in subjects with ACS presenting with STEMI or NSTEMI and MVD, while subjects have not died due to non-CV causes.

The following algorithm will be applied to derive two analysis variables, one corresponding to time in days and a second corresponding to censoring status. Any death with cause adjudicated as "undetermined" will be included as CV death in the primary analysis. The table below gives the derivation algorithm to be used in the primary analysis.

	Time to Event (days) [TTE]	Censoring Status [Censor]
First of confirmed CV death, MI, or Stroke during 90 days following randomization	(date of MACE – randomization date) + 1	0
Last MACE ascertainment on or after 90 days of follow-up without experiencing MACE	90	1
Discontinue prior to 90 days without experiencing MACE	(date of last MACE assessment – randomization date) + 1	1
Experience non-CV death prior to day 90	(date of death – randomization date)+1	1

All events of CV death, MI, and stroke occurring beyond the completion of the 90-day window will be excluded from the primary efficacy analysis, but will be collected, adjudicated and analyzed as secondary endpoints.

The primary endpoint will be descriptively summarized including the number (%) of subjects experiencing MACE, number administratively censored at 90 days; of the non-administratively censored subjects, number lost to follow-up and number experiencing a non-CV death. Event counts and incidence rates will be summarized including point estimates and 95% CIs by treatment group. Cumulative MACE rates through 90 days will be calculated using the Kaplan-Meier method. The effect over time will be illustrated with a plot of the complement (1 - KM) of Kaplan-Meier estimates. A data listing of time to first MACE with an indicator of event or censored time will be produced.

A covariate-adjusted Cox proportional hazards regression model including fixed effects for treatment, region, index MI, index MI management, age (as a continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and index MI management will be fitted using the PHREG procedure in SAS. The covariates represent stratification factors (region, index MI, index MI

management) and study enrichment factors (age, diabetes, peripheral artery disease, history of MI) which are well-established prognostic variables. The SAS code fragment for fitting this model is shown in Appendix 15.5. The results for time to first MACE will be summarized in a table including number (%) of subjects with events, estimated hazard ratio, 95% CI and 1-sided Wald *P* value.

The validity of the proportional hazards assumption will be investigated by examining a plot of the log-cumulative hazard versus log of survival time for the treatment effect. The assumption will be considered to hold if the resulting curves are approximately parallel and do not cross. If the proportional hazards assumption does not hold, an appropriate sensitivity analysis will be performed.

Concordance (%) between the CEC adjudicated and investigator-reported primary MACE components through study Day 90 and end of study will be descriptively summarized. The extent of agreement will be summarized in two different ways as described below:

- As a percentage of total number of investigator-reported cases: the numerator is the number of positively adjudicated investigator-reported events and the denominator is the number reported by investigator.
- As a percentage of total number of adjudicated cases: the numerator is the sum of positively adjudicated investigator-reported events and negatively-adjudicated events based on trigger terms while the denominator is the total number of adjudicated cases (positive and negative). Trigger terms are suspected MACE identified from a review of reported adverse events by sponsor and are not investigator-reported.

10.1.1 Sensitivity/Supportive Analyses of Primary Endpoint

Additional sensitivity analyses of the primary endpoint will be performed to assess the robustness of conclusions from the planned, primary analysis to deviations from assumptions. Consistency of findings from the primary and sensitivity analyses will be investigated and clinical plausibility of findings from sensitivity analyses will be examined. Sensitivity analyses will be performed in the following categories:

- Informative Censoring: The primary analysis is planned to be performed under the assumptions that observations are censored-at-random (CAR) and that censoring is uninformative; meaning that censoring times and event times are independent. There is no plan to impute missing event times in the primary analysis.

The tipping point analysis, based on the pattern mixture model (PMM) approach [Lipkovich et al, 2016] will be used as a sensitivity analysis to examine the effect of potential departures from the CAR assumption in the primary analysis. For non-administratively censored subjects, missing event times in the placebo arm will be imputed from completers in the same treatment arm using a CAR assumption whereas missing event times in the CSL112 arm will be imputed under increasingly higher hazards of MACE to determine whether the conclusion from the primary analysis can be nullified. The implication being that the non-administratively censored subjects on CSL112 have a worse outcome from the time of censoring, compared with similar subjects who remain in the study. This worsening outlook is quantified by a sensitivity parameter δ interpreted as an increased hazard of MACE post-dropout. The goal of the tipping point analysis is to increase the value of δ in the non-administratively censored CSL112 subjects until the conclusion from the primary analysis is nullified. The clinical plausibility of obtaining such a value of δ will be assessed. Hazard ratios and 95% CIs for the hazard ratio corresponding to each value of δ will be presented in a similar manner as described under the primary analysis. The SAS/PROC PHREG code fragment for generating samples from a Bayesian joint posterior distribution and associated options is given in Appendix 15.5.

The tipping point analysis will be based on multiple imputations from a piecewise exponential proportional hazards model [Lipkovich et al, 2016] consisting of four intervals (≤10 days, >10 to ≤30 days, >30 to ≤50 days and >50 days) over which the piecewise constant baseline hazard is defined. The analysis and implementation models are expected to include the same set of explanatory variables as the primary analysis unless cells with zero events in the interaction term (between index MI type and management type) are encountered during analysis in which case the interaction term will be omitted from both the imputation and analysis models.

- Reduced statistical model – This analysis will be conducted without the prognostic variables which are included in the primary model, i.e. age ≥ 65 years, diabetes, peripheral artery disease, or history of prior MI [excluding index MI]. The statistical analysis will be based on a covariate-adjusted Cox proportional hazards regression model including fixed effects for treatment, region, index MI type, index MI management, and a term for interaction between index MI type and index MI management. Thus, this model adjusts only for stratification factors and not for prognostic factors.

- Unadjusted statistical model – In this analysis, the primary efficacy endpoint will be analyzed based on a Cox regression model including a covariate for treatment only.

- Receipt of investigational product – Sensitivity of results to whether the subject received any amount of the investigational product will be investigated by analyzing the primary endpoint based on the modified intent-to-treat (mITT) Analysis Set where the estimand is defined as the hazard ratio for CSL112 vs. placebo, among subjects receiving at least one infusion, in addition to SOC as taken, for time to first occurrence of CV death, MI or stroke through 90 days in subjects with ACS presenting with STEMI or NSTEMI and MVD, while subjects have not died due to non-CV causes. While this is not the primary analysis, this could be considered to be most meaningful, as it assesses treatment effect among all subjects who received at least one dose of study medication.

- Compliance with receipt of investigational product – sensitivity of results to whether subjects receive infusions in compliance with the study protocol will be investigated based on a per-protocol estimand [ICH E9 (R1)] defined as hazard ratio for CSL112 vs. placebo, among subjects receiving infusions as scheduled, in addition to standard of care as taken, for time to first occurrence of CV death, MI or stroke through 90 days in subjects with ACS presenting with STEMI or NSTEMI and MVD, while subjects have not died due to non-CV causes. Subjects with missed dose or treatment discontinuation will be censored 7 days (or less if next infusion is administered <7 days apart) after last infusion received on schedule. Subjects receiving no infusions will be censored at the time of randomization.

10.1.2 Subgroup Analyses of Primary Endpoint

Internal consistency of observed treatment effect on the time to first primary MACE will be explored across major subgroups including at a minimum, but not limited to, those shown in the list below. The description and numeric coding of subgroup levels for analysis is given in Section 8.2.9.

- Age: <65 years, ≥65 years
- Gender: Female, Male
- Race: White, Black, Asian, Other
- Ethnicity: Hispanic, non-Hispanic
- Region (1): North America, Latin America, Western Europe, Central and Eastern Europe, and Asia Pacific
- Region (2): North America (U.S. and Canada), Rest of the World (RoW)
- Type of Index MI (ACS type): STEMI, NSTEMI as randomized (primary)

- Type of Index MI (ACS type): STEMI, NSTEMI as per last recorded value (supplemental)
- Index MI Management: PCI or medically managed as randomized (primary)
- Index MI Management: PCI or medically managed as per last recorded value (supplemental)
- Diabetes Mellitus on Pharmacotherapy: Yes or no
- Prior MI: Yes or no
- Prior PCI: Yes or no
- Meet modified enrichment criteria: Yes or no
- Peripheral Artery Disease: Yes or no
- Renal function: eGFR ≥90 mL/min/1.73 m^2 (normal renal function), eGFR ≥60-<90 mL/min/1.73 m^2 (mild renal impairment), eGFR ≥30 - <60 mL/min/1.73 m^2 (moderate renal impairment)
- HDL Cholesterol:
    - Low or normal, definition based on gender-specific cut points: <1.04 µmol/L (<40 mg/dL) for men and <1.3 µmol/L (<50 mg/dL) for women
    - Subgroup definition based on tertiles of HDL cholesterol reported at screening
- Planned staged PCI: Yes or no
- Medication usage at the time of index MI
    - Thrombolytic agents: yes or no
- Medication usage by drug class at randomization:
    - Aspirin: Yes or no
    - PCSK9 inhibitors: Yes or no
    - P2Y12 inhibitors: Yes or no
    - Non-statin lipid modifying agents: Yes or no
    - Statins by dose intensity: High, non-high, and none
    - SGLT2 inhibitor: Yes or no
- Treatment group comparisons within each of the additional subgroups defined below based on the primary MACE endpoint and all-cause mortality through 365 days from randomization:
    - PCI/STEMI
    - PCI/NSTEMI
    - Thrombolytic use/STEMI
    - No-thrombolytic use/STEMI
    - No-thrombolytic use/NSTEMI

  The PCI category includes any subject with a PCI; the thrombolytic category includes subjects receiving thrombolytics for the index MI but excludes subjects with a PCI

and the no thrombolytic category excludes subjects with a PCI or receiving thrombolytics. This subgroup reflects a transformation of the stratification factor, index MI management type, from two levels (PCI/medically managed) to three levels (PCI, thrombolytic use and no thrombolytic use). A new variable with 5 levels, as given in the bulleted list above will be derived and used as a covariate in the model.

- Treatment group comparisons within each of the additional subgroups defined below based on the primary MACE endpoint and secondary efficacy endpoints:
  - PCI
  - Thrombolytic use
  - No-thrombolytic use
- Enrollment cohort relative to communication date of sample size re-estimation to investigators: Before or after
- Number of hours from FMC to the first infusion – above (>) or below (≤) the median time from FMC to first infusion
- Enrollment under the original protocol or amendment 1

Subgroup analysis will be based on a covariate-adjusted Cox proportional hazards model including fixed effects for treatment, stratification factors, age, diabetes, peripheral artery disease, history of prior MI (excluding index MI), subgroup, and interaction terms for treatment by subgroup as well as index MI type by management type. The exceptions to this list of covariates apply to the subgroup analyses listed below:

- Subgroup by Age – will omit inclusion of age as a continuous covariate
- Subgroup by Index MI type - omit the interaction term *index MI by management type*
- Subgroup by Management type – omit the interaction term *index MI by management type*
- Subgroup PCI/Thrombolytic use/No thrombolytic use – omit model term for index MI management type and interaction *index MI by management type*
- Subgroup defined based on a combination of index MI type and management type (excluding NSTEMI/Thrombolytic use) – omit model terms for index MI type, index MI management type and interaction between *index MI type by management type*

One model per subgroup will be fitted. The following displays will be provided for time to first primary MACE subgroup analyses:

- A summary for each level of subgroup, including the number (%) at risk, number (%) with events, hazard ratio and 95% CI and a two-sided Wald *P* value for the interaction term. Counts and percentages of subjects with events will be displayed at each level

of the subgroup. The total number of subjects at each subgroup level will serve as the denominator for percentages. However, only subgroups with non-zero events in both treatment arms will be included in the analysis model.

- A forest plot of subgroups with hazard ratio and 95% CI displayed for each level of subgroup

10.1.3 Interpretation of Subgroup Analyses

Within this study, factors defining subgroups are classified into the following two categories:

1. Key Subgroups: A factor for which there is some biological plausibility or external evidence such that an inconsistent response might be observed. This category includes factors used to stratify the randomization, as well as other subject characteristics.
2. Exploratory Subgroups: A factor for which there is good argumentation why consistency of response to treatment is plausible.

Factors defining key subgroups (i.e. those belonging to category 1 above) are listed in the table below:

Factor Defining Key Subgroups	Rationale for Designation as "Key"
Index MI type (STEMI vs NSTEMI)	Stratification factors
Management of the index MI (percutaneous coronary intervention versus medically managed)	
Region (North America, Latin America, Western Europe, Central and Eastern Europe, or Asia Pacific)	

The assessment of relevant subgroups is an important step to support the conclusion that the treatment effect applies to the potentially heterogeneous population of a trial. No formal rule for the interpretation of subgroup findings, which is both sensitive to detect inconsistency in treatment effects and specific to avoid false-positive findings, is available.

The "credibility" flowchart provided in Appendix 15.4 will be followed for purposes of interpretation. Since the CSL112 development program includes a single pivotal outcomes trial supporting registration, and no relevant external data exists, there is no possibility of replicating subgroup analysis results to ascertain consistency across trials. An assessment of credibility will consider the estimate and precision of the overall effect, the estimate and confidence interval of the subgroups, the p-value for the test of interaction, and the clinical

relevance. Inconsistencies in treatment effect of primary concern are those which are qualitative, ie, those for which the treatment effect is directionally different in the subgroup.

If evidence of inconsistency is observed in a “key subgroup”, where there is biological plausibility for an inconsistent effect in the direction expected, it may be considered credible, and hence subject to further sponsor evaluation and regulatory consideration.

In the case where there is no biological plausibility for a differential treatment effect in the subgroup, ie for an “exploratory subgroup”, but a differential effect is observed, an assessment will be made as to whether the evidence is statistically or clinically extreme. If the evidence is not statistically or clinically extreme, the differential treatment effect will be considered as not credible. Further details and rationale are provided in Appendix 15.4.

10.2 Analysis of Key Secondary Endpoints

The key secondary endpoints will be analyzed based on the ITT population. The null hypothesis associated with each key secondary endpoint will be tested at the time of final analysis. The analysis will be based on CEC-adjudicated events and an assessment of concordance between the investigator-reported and CEC adjudicated events will be undertaken. Multiplicity adjustments are discussed in Section 7.4.

The three key secondary endpoints and their planned analyses are given below:

10.2.1 Total number of hospitalizations for coronary, cerebral, or peripheral ischemia through 90 days after randomization

A negative binomial regression model will be fitted to the count data arising from the number of hospitalizations. This analysis will consider only those hospitalizations adjudicated by the CEC as meeting endpoint criteria. The model will include fixed effects for treatment, region, index MI type, and index MI management, age (as a continuous variable), diabetes, peripheral artery disease, and history of MI, and a term for interaction between index MI type and index MI management which correspond to the covariates in the primary analysis. The log link function will be used and the log-transformed duration of follow-up (based on the date of last MACE ascertainment) within 90 days will be included in the model to account for the variable duration of follow-up across subjects. However, if the model fails to converge then the offset statement will be excluded. The mean rate of hospitalization per 90 days will

be presented by treatment arm. A 1-sided *P* value for treatment comparison, the rate ratio (CSL112: placebo) and its 95% CI will be estimated from the model.

A cumulative plot of recurrent hospitalization events will be generated using a non-parametric estimator for the mean cumulative function (MCF). Nelson [Nelson, 2003] introduced the MCF as a way to summarize the average number of events occurring in a subject by time t, within a population exposed to censoring events such as losses to follow-up and termination of the study. It assumes non-informative censoring and the risk set decreases only when an individual is removed from follow-up. A supportive data listing of hospitalization data will be produced.

The SAS code for fitting a negative binomial regression model to the count data from hospitalizations is given in Appendix 15.5.

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

The leading analysis of the hospitalizations endpoint described above is focused on the estimation of a rate ratio (CSL112: placebo) to determine whether treatment with CSL112 reduces the mean number of hospitalizations during the 90 day period. This approach accounts for death indirectly by adjusting the mean incidence for the duration of exposure but otherwise ignores death in the analysis. Thus, it provides a pharmacoeconomic assessment of treatment benefit afforded by CSL112.

A sensitivity analysis of the hospitalization data will be performed to explicitly incorporate death into the outcome using the Win Ratio [Pocock et al, 2012] method. This approach recognizes clinical hierarchies within composite outcomes. With the planned endpoint, death will be weighted more heavily relative to the total number of CV hospitalizations during 90 days from the time of randomization. The Win Ratio (CSL112: Placebo) will be calculated along with associated 95% CI and a 1-sided *P* value. A complete description of the analytical approach is given in Appendix 15.1.

10.2.2 Time to first occurrence of CV Death, MI, or stroke from the time of randomization through 180 days

The derivation of time to first occurrence of CV Death, MI, or stroke from the time of randomization through 180 days is given below. The analytical details are similar to that described for the primary efficacy endpoint and hence a general description is given here.

	Time to Event (days) [TTE]	Censoring Status [Censor]
First of positively adjudicated CV Death, MI, or stroke during the 180 days following randomization	(date of MACE – randomization date) + 1	0
Last MACE ascertainment on or after 180 days of follow-up without experiencing MACE of interest (administrative censoring)	180	1
Discontinue prior to 180 days without experiencing MACE	(date of last MACE assessment – randomization date) + 1	1
Experience non-CV death prior to day 180	(date of death – randomization date)+1	1

Cumulative event rate through 180 days will be calculated using the Kaplan-Meier method. The summary will include the number of subjects with events, number administratively censored as well as number of non-administratively censored subjects. The effect over time will be illustrated with plot of the complement (1 - KM) of Kaplan-Meier estimates. Event counts and incidence rates will be summarized including point estimates and 95% CI s by treatment group.

A covariate-adjusted Cox proportional hazards regression model including fixed effect for treatment, region, index MI type, index MI management, age (as a continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI), and a term for interaction between index MI type and index MI management will be fitted to the data based on the PHREG procedure in SAS. The results from the Cox model will be summarized in a table including number (%) of subjects with events, estimated hazard ratio for treatment, its 95% CI and a 1-sided Wald *P* value for treatment comparison.

A supportive listing of individual subject data including the time to event in days and the censoring variable will be presented.

10.2.3 Time to first occurrence of CV Death, MI, or stroke from the time of randomization through 365 days

The analytical approach as outlined in Section 10.2.2 will also be applied to time to first occurrence of CV death, MI, or stroke from the time of randomization through 365 days.

A tipping point analysis will be performed to assess the impact of missing follow-up time in subjects who complete the study earlier than study day 365. Missing event times in the placebo arm will be imputed from subjects completing 365 days of follow-up under a CAR assumption while missing event times in the CSL112 arm will be imputed under increasing hazards of MACE (δ) to ascertain whether the conclusion from the leading analysis of the endpoint can be nullified. The clinical plausibility of the delta value at the tipping point, if reached, will be assessed. Hazard ratios and 95% CIs corresponding to each value of delta will be summarized.

10.3 Analysis of Other Secondary Efficacy Endpoints

The list of other Secondary Efficacy Endpoints is shown below. These endpoints are not included in the formal hypothesis-testing framework and as such are not part of the Hochberg procedure described in Section 7.4. The *P* values are intended to be descriptive. The analysis of the secondary efficacy endpoints will be based on the ITT Analysis Set.

1. The time to first occurrence of each individual component of the composite primary efficacy endpoint
    - Time to occurrence of CV death from the time of randomization through 90 days
    - Time to first occurrence of MI from the time of randomization through 90 days
    - Time to first occurrence of stroke from the time of randomization through 90 days

The planned analysis of the components is not designed to take competing risks into consideration. For example, in the analysis of time to occurrence of MI, CV death will be censored. Computationally, this approach is equivalent to the cause-specific hazard ratio that would be obtained for MI in a competing risks framework.

2. Time to occurrence of CV death, Type 1 MI, or stroke from the time of randomization through days 90, 180, and 365
3. Time to occurrence of all-cause death from the time of randomization through 365 days

In the analysis of time to all-cause death (ACD), censoring will be based on the vital status assessment at Day 365 for subjects not completing the study. If subject is alive at Day 365, then subjects will be censored at the time point of interest (days 90, 180, 365). In the analysis of ACD through the end of study, subjects will be censored at Day 365. If Day 365 vital status is unknown, subjects will be censored at the date of last MACE ascertainment.

The analytical approach for the time-to-event endpoints listed above will be similar to that described for the primary endpoint in Section 10.1.; ie, estimates of the 1-sided Wald *P* value, the hazard ratio and associated 95% CI s will be obtained from a covariate-adjusted Cox proportional hazards regression model with fixed effects for treatment, region, index MI type, index MI management, age (as a continuous variable), diabetes, peripheral artery disease, history of prior MI (excluding index MI) and a term for interaction between index MI type and index MI management in the model. The *P* values are intended to be descriptive. The effect over time will be illustrated with the complement of (1 - KM) of Kaplan-Meier estimates. Event count (%) will be presented.

A supportive listing of individual subject data including the time to event in days and the censoring variable will be presented.

10.4 Analysis of Exploratory Endpoints

The following set of exploratory endpoints is planned in this study. *P* values are intended to be descriptive. The analysis of the exploratory endpoint will be based on the ITT population.

1. Total number of hospitalizations for coronary, cerebral, or peripheral ischemia from the time of randomization through 30 days
2. Time-to-first occurrence of CV death, MI, or stroke or severe coronary ischemia requiring urgent revascularization from the time of randomization through 90 days
3. Time to first occurrence of CV death, MI, or stroke from the time of randomization through 30 and 60 days
4. Time to first occurrence of MI by type, according to universal definition, from the time of randomization through 90 days
5. Time to occurrence of CV death from the time of randomization through 365 days
6. Time to occurrence of non-CV death from the time of randomization through 365 days

7. Total occurrence of rehospitalization for CV events and all-cause death from the time of randomization through 90 days. Rehospitalization is defined as any site-reported post-index MI hospitalization (including extension of index MI hospitalization past randomization date due to a treatment-emergent serious adverse event) that is adjudicated, regardless of adjudication outcome, or a positively adjudicated triggered event linked to a site-reported adverse event. Urgent heart failure visits with a less than 24 hour stay are not considered.
8. Total occurrence of all-cause death, MI, and stroke from the time of randomization through 90,180 and 365 days
9. Total occurrence of CV death, MI, and stroke from the time of randomization through 90, 180, and 365 days
10. Medical resource utilization from the time of randomization through 90 days:
    a. Number of total hospitalizations
    b. Length of hospital stay
    c. Number of cardiac care unit (CCU) or intensive care unit (ICU) days
    d. Select surgeries / select procedures related to hospitalization for coronary, cerebral, or peripheral ischemia (see Section 9.5 for definition)
    e. Discharge to: home with additional care, home without additional care, rehabilitation or skilled nursing facilities following hospitalization for coronary, cerebral, or peripheral ischemia
11. Change in EQ-5D-3L data from baseline to day 90

The planned analyses of the exploratory efficacy endpoints are given below in the same order as the list of endpoints above.

The hospitalizations for coronary, cerebral, or peripheral ischemia through 30 days from the time of randomization, will be analyzed similarly to the key secondary endpoint of hospitalizations through 90 days following randomizations based on a negative binomial regression model.

The exploratory time to event efficacy endpoints listed in 2 through 6 above will be analyzed in a similar manner to that of the primary endpoint. Pre-planned staged PCIs will be excluded in the analysis of the endpoint time to first occurrence of CV death, MI, stroke, or severe

coronary ischemia requiring urgent revascularization. Treatment comparison will be based on a covariate-adjusted Cox regression model for estimating the 1-sided *P* value, the hazard ratio and its 95% CI. The effect over time will be illustrated with a plot of the complement (1 - KM) of the Kaplan-Meier estimates. Event counts (%) will be presented.

The analysis of the total occurrence of rehospitalization (post-index MI) and all-cause death through 90 days will be based on Win Ratio methodology [Pocock et al, 2012] as described in Section 10.2.1. In this analysis, clinical hierarchy is defined as all-cause death followed by hospitalization. The Win Ratio (CSL112: Placebo) will be calculated along with associated 95% CI and a 1-sided *P* value. A complete description of the analytical approach is given in Appendix 15.1. Total occurrence of rehospitalization will also be analyzed utilizing a negative binomial model as described previously.

The exploratory endpoints including total occurrence of CV death, MI, and stroke from time of randomization through 90, 180, and 365 days and total occurrence of all-cause death, MI, and stroke from randomization through 90, 180, and 365 days will be analyzed using a negative binomial regression model in a similar manner as described in Section 10.2.1 for the number of hospitalizations through 90 days.

For each exploratory endpoint based on CEC adjudicated outcomes, summary table of consistency of findings between the CEC and investigator-reported MACE will be produced as given in Section 10.1. A supportive listing of individual subject data including the time to event in days and the censoring variable will be presented.

The relationship between medical resource utilization and treatment with CSL112 will be descriptively summarized. The endpoints of medical resource utilization including the number of hospitalizations, length of hospital stay (days), CCU or ICU stay (days) and number of select surgeries/select procedures related to hospitalization for coronary, cerebral, or peripheral ischemia will be treated as count data for the purpose of analysis. For each subject, total counts either in number of admissions or duration of stay will be derived across all hospitalizations occurring during the 90 day period from randomization. The analyses of these endpoints will use a negative binomial regression model as described for the key secondary endpoint of CV hospitalizations described in Section 10.2.1. Discharge to following CV hospitalization will be descriptively summarized with counts and percentages in each category by treatment arm.

The EQ-5D-3L is a patient self-assessment of five dimensions of health-related quality of life: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each dimension is measured on a 3-point scale where a higher score corresponds to a worse health state. Scores from the individual dimensions will be used to calculate an overall utility score for each patient using the algorithm specified by the developers of the instrument [EuroQoL, 2015]. The EQ VAS is a continuous 100 point integer scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine). Further details can be found in Appendix 15.2.

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

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

Additional Exploratory Efficacy Endpoints

The following additional exploratory efficacy endpoints will be analyzed based on the ITT population. Endpoints consisting of other time points (90, 180, or 365 days) not explicitly listed in this document will also be analyzed.

1. Time-to-occurrence of all-cause death from the time of randomization through 90, 180 days and end of study

2. Time to occurrence of non-COVID-19 related death from the time of randomization through day 365. All deaths resulting from COVID-19 will be censored in this analysis

3. Time-to-first occurrence of CV death or MI from the time of randomization through 90 days

4. Time to first occurrence of CV death, MI, or stroke from the time of randomization through the end of study

5. Time-to-first occurrence of all-cause death, MI, or stroke from the time of randomization through 90 days

6. Time to occurrence of CV death from the time of randomization through 180 days and end of study

7. Time-to-first occurrence of MI from the time of randomization through 180, 365 days and end of study

8. Time-to-first occurrence of stroke from the time of randomization through 180, 365 days and end of study

9. Time to occurrence of thrombotic (ischemic) strokes with hemorrhagic conversion from the time of randomization through day 365

10. Time to occurrence of hemorrhagic stroke from the time of randomization through day 365

11. Time-to-first occurrence of stroke including sub-arachnoid stroke from the time of randomization through days 90, 180 and 365

12. Medical resource utilization from the time of randomization through 180 and 365 days:
    a. Number of total hospitalizations
    b. Length of hospital stay
    c. Number of cardiac care unit (CCU) or intensive care unit (ICU) days
    d. Select surgeries/select procedures related to hospitalization for coronary, cerebral, or peripheral ischemia

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

13. Assessment of neurological disability using the Modified Rankin Score

The time to event endpoints in 1 through 11 will be analyzed similarly to the primary endpoint (see Section 10.1) while endpoints listed in 12a through 12d will be analyzed using a similar approach described in Section 10.2.1 for the analysis of total number of hospitalizations for coronary, cerebral, or peripheral ischemia. The endpoint 12e will be descriptively summarized with counts and percentages of subjects in each category. The endpoint listed in 13 utilizes a rating scale of neurological disability ranging from 0 to 6, with 0 = total lack of symptoms,1 = no significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death. Subjects experiencing stroke during the course of the study will be graded to reflect the extent of neurological dysfunction. Descriptive summaries will be generated as follows: counts and % of subjects each level and also as a collapsed value (0-2; not disabling) vs. (3-6; disabling).

10.5 Treatment Compliance

The compliance with the study treatment will be summarized at each infusion and overall.

A subject is considered to be compliant with the investigational product if at least 80% of investigational product is administered. The portion of investigational product administered is determined using the algorithm $\left(\frac{actual\ volume\ infused}{planned\ volume}\right)$*100%.

A binary variable (yes/no), associated with each infusion, will be defined to determine whether or not a subject is compliant. A subject will be considered to be compliant overall if each dose administered for that subject is compliant.

At each of the four infusions, number of subjects receiving the infusion, number compliant, and the portion of IP administered will be summarized. At infusions 2-4, the time interval between successive doses will be categorized as <5 days and ≥5 days; the number (%) of subjects in each interval will be presented. The number of days between successive doses will also be summarized as a continuous variable.

The following listing will be provided:

- Compliance with individual infusions and across all infusions overall

11 Safety Analyses

All analyses described in this section will be based on the Safety Analysis Set as defined in Section 6.5.

11.1 Extent of Exposure

The extent of exposure to the study treatment will be summarized based on the Safety Analysis Set.

A cross tabulation of treatment randomized and treatment received will be generated. The treatment received category will also include randomized but not treated subjects.

Exposure to the investigational product will be descriptively summarized overall:

- Number of infusions (partial or complete) administered per subject
- Number of complete infusions administered per subject where a complete infusion is defined as receipt of at least 80% of planned infusion

Following data will be summarized for each infusion:

- Volume of infusion (mL) including any interruption(s)
- Duration of infusion (hours)
- Number of subjects with 0, 1, 2, or 3 or more infusion interruptions
- Cumulative duration of interruption (hours)
- Location of infusion administration including hospital, infusion center, or doctor's office or clinic

IP Overdose is defined as any single infusion with an infusion volume exceeding 150% the planned volume (170*1.5 = 255 mL) or an infusion rate that exceeds 3 mg of sucrose/body weight (kg)/duration of infusion (min) where infusion rate is calculated as (actual infused volume/170)*9900/(duration of infusion*weight). The 6g dose of CSL112 contains 9.9 g or 9900 mg of sucrose. The total number of subjects experiencing overdose will be presented by counting subjects once regardless of the number of overdoses that occur for a given subject.

The listing of individual subject data will include all variables presented in the summary table.

11.2 Adverse Events

Verbatim adverse event terms reported by investigator will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA) dictionary. SAS datasets containing Standard MedDRA Queries (SMQs) will be generated directly from the MedDRA dictionary and merged with investigator-reported data by preferred term to identify occurrences of specified groupings of adverse events.

The planned periods of observation, starting with the time of written informed consent, for collecting AEs in this study are described below:

- All AEs through Visit 8/Day 90, regardless of relationship to the investigational product
- AEs related to the investigational product through the end of study
- AEs leading to discontinuation and AEs leading to withdrawal of consent through the end of the study
- All SAEs will be collected through the end of the study, regardless of relationship to investigational product

All adverse and clinical (suspected MACE) events will be entered on the AE / SAE eCRF form utilizing an appropriate event category. In order to distinguish between clinical events (which are adjudicated, and analyzed/reported as efficacy endpoints) and adverse events occurring during the study, an AE flag variable will be derived as described below. All adverse events where the flag is set to Yes will be included in the estimation of AE incidence rates.

Set AE Flag=*No* if:

- AE outcome = fatal and adjudicated as CVD or undetermined cause of death
- AE outcome non fatal, reported by site as a CV endpoint, adjudication by the CEC as meeting CV endpoint criteria
- AE outcome non fatal, reported by site as an AE, triggered adjudication by the CEC as meeting CV endpoint criteria

11.2.1 Treatment-emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs occurring on or after the start date of the first infusion. AE severity is determined on a scale from mild, moderate to severe.

An overview summary of all TEAEs will be summarized as described below. The number (%) of subjects experiencing events in each category will be displayed by treatment group.:

- Any TEAE through day 90 / through end of study
- TEAEs that begin within 24 hours of start of an investigational product infusion
- TEAEs that begin after 24 hours from the start of investigational product infusion and are related to study treatment
- TEAEs that are related to investigational product, irrespective of start time
- Non-fatal TEAEs leading to permanent discontinuation of investigational product (ie, TEAEs that cause permanent cessation of all further study treatment)
- Non-fatal TEAEs leading to withdrawal from study
- TEAEs leading to dose interruptions (ie, TEAEs which occur during an infusion and cause that infusion to be temporarily or permanently halted)
- TEAEs leading to skipped infusions (ie, TEAEs which do not resolve in time to allow all 4 infusions to be administered within 30 days)
- SAEs
- SAEs related to study treatment
- Fatal SAEs
- Fatal SAEs related to study treatment
- TEAEs of special interest including drug hypersensitivity, acute kidney injury, potential hepatic injury, and new onset or worsening of heart failure

Non-TEAEs will be included in a data listing but not in a summary table.

The following summaries of TEAEs will be presented and will display the number of subjects and the number of events. With the exception of summary tables by worst severity (described further below), subjects with multiple occurrences of the same TEAE will be counted once; however, all occurrences of the TEAE will be reflected in the event count. In the summary tables by worst severity, subjects will be counted once in the most severe category at overall, SoC, and each unique PT level. Multiple occurrences of the same PT with the same severity are all counted at overall, SoC, and PT levels; however, multiple occurrences of the same PT with different severities are counted in the most severe category at overall, SoC and PT levels. The frequency and percentage of TEAEs will be summarized and displayed in two

ways: 1) in descending order of incidence in CSL112 arm by System Organ Classes (SOC) and PT and 2) in descending order of incidence in CSL112 arm by PT only. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once. The following summaries will be provided as described above:

- All Treatment-Emergent Adverse Events through day 90 by SoC and PT
- All Treatment-Emergent Adverse Events through end of study by SoC and PT
- All Treatment-Emergent Adverse Events through day 90 by Worst Severity, SoC and PT
- All Treatment-Emergent Adverse Events through end of study by Worst Severity, SoC and PT
- All Treatment-Emergent Adverse Events through day 90 by PT
- All Treatment-Emergent Adverse Events through end of study by PT
- All Treatment-Emergent study treatment-related Adverse Events, SoC and PT
- Study treatment-related TEAEs with onset after the start of infusion of investigational product. Missing relationship to study treatment will be imputed as described in Section 8.1.3; this summary will also include the number and percentage of TEAEs with a missing relationship to aid in interpretation of the results.

The following listing will be provided:

All Adverse Events - this listing will include treatment, stratification factors, age, sex, race, SoC, PT, verbatim term, Start, End, and duration, severity, serious (yes or no), relationship to treatment (yes or no), outcome, and action taken.

11.2.2 Adverse Events of Special Interest (AESI)

The following TEAEs are considered to be of special interest:

- Hypersensitivity : SMQ narrow 20000214 for Hypersensitivity will be used to identify the relevant preferred terms. The following summary tables will be produced.
  - An overview of adverse events related to hypersensitivity
  - Hypersensitivity by PT
  - Hypersensitivity by PT separately for serious and non-serious AEs

- Treatment-related hypersensitivity by PT
- Treatment-related serious hypersensitivity events by PT

- Acute kidney injury (AKI):
  - This AESI is defined based on central laboratory values. Any increase in serum creatinine value of ≥27 µmol/L (0.3mg/dL) from the baseline serum creatinine during the Active Treatment period will be considered an AESI.
  - Any increase in serum creatinine value of ≥27 µmol/L (0.3mg/dL) from the baseline serum creatinine on two consecutive occasions during the Active Treatment period will also be summarized.
  - Relevant preferred terms based on MedDRA SMQ Acute Renal Failure, narrow 20000003 will be summarized to provide additional, supportive analyses of kidney safety/injury and will include the following summaries:
    - An overview of AKI events
    - AKI events by PT
    - Serious AKI events by PT
    - Non-serious AKI events by PT
    - Treatment-related AKI events by PT
    - Treatment-related serious AKI events by PT
- Potential hepatic injury (PHI):
  - This AESI is defined based on central laboratory values. Occurrence of either concomitant elevations of ALT > 3 x ULN with TBili > 2 x ULN, or ALT > 5 x ULN at any time during the study will be considered an AESI.
  - Potential drug-induced liver injury (DILI) will be adjudicated by the CEC. Number (%) of subjects with a positively-adjudicated event will be summarized. The CEC adjudication process will include both central and local lab results.
  - A supporting table of AESI as described in the first bullet including both central and local lab results.
  - Supporting summaries of hepatic events by PT where events will be identified using the following MedDRA SMQs:
    - Cholestasis and jaundice of hepatic origin (SMQ) [20000009] – Broad

        - Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) [20000013] – Broad
        - Hepatitis, non-infectious (SMQ) [20000010] – Broad
        - Liver related investigations, signs and symptoms (SMQ) [20000008] – Broad
    - The summary tables of AEs related to PHI will include the following:
        - Overview of PHI events
        - PHI events by PT
        - Serious PHI events by PT
        - Non-serious PHI events by PT
        - Treatment-related PHI events by PT
        - Treatment-related Serious PHI events by PT
- New or worsening heart failure – will be adjudicated by the CEC. The number (%) of subjects positively adjudicated will be reported.

A summary table will be provided to present the number (%) of subjects experiencing each AESI by treatment group along with point and 95% CI [Newcombe, 1998] estimates for the treatment difference.

Supportive data listings will be produced for each AESI.

11.2.3 Serious Adverse Events

The following summaries will be presented by treatment arm, SOC, and PT.

- Treatment-Emergent SAEs
- Study Treatment-Related SAEs
- Treatment-Emergent SAEs with a fatal outcome
- Study Treatment-Related SAEs with a fatal outcome

The following listings will be provided:

- All Treatment-Emergent SAEs
- Treatment-Emergent SAEs with a fatal outcome

11.2.4 Deaths

CEC-adjudicated deaths will be summarized by displaying the number and percentage of subjects within categories of CV and non-CV death. All deaths adjudicated with an undetermined cause of death will be analyzed as CV death. Deaths among screen failed subjects will be listed separately.

11.2.5 Adverse Events Leading to Discontinuation of Study Treatment, Withdrawal from the Study, and Other Significant Adverse Events

The following categories of treatment-emergent AEs will be summarized:

- Treatment-Emergent AEs Leading to Discontinuation of Study Treatment
- Treatment-Emergent AEs leading to Withdrawal from the Study
- Treatment-Emergent AEs Leading to Infusion Interruptions

The following listings will be provided:

- Treatment-Emergent AEs Leading to Discontinuation of Study Treatment
- Treatment-Emergent AEs leading to Withdrawal from the Study
- Treatment-Emergent AEs Leading to Infusion Interruptions

11.3 Adverse Events Meeting Pre-specified Criteria:

Adverse events meeting at least one of the following criteria, as specified by the FDA, in communication with CSL, for identification of potential adverse drug reactions, will be reported by SoC and PT. A separate tabular summary will be generated for each of the four bullets below as well as a combined summary of all AEs meeting the pre-specified criteria:

1. AEs that begin within 24 hours after the start of an infusion
2. AEs that begin more than 24 hours after the start of infusion and reported as at least possibly causally related to the administration of study treatment by the investigator or sponsor. It is noted however that the reference to sponsor assessment of causality is part of the FDA definition but this information is not captured in the clinical database.
3. AEs for which the investigator's causality assessment is missing or indeterminate

4. Exposure adjusted incidence of TEAEs: all AEs, for which the incidence in an active treatment arm exceeds the exposure-adjusted incidence rate in the placebo arm by 30% or more on a relative basis, provided the difference in incidence rates is 1% or more. The algorithm is shown below:

For each PT recorded on the AE page of the eCRF, the following algorithm will be applied to define whether or not the PT in question meets the criterion defined in bullet 4.

Incidence Rate (IR) = $\frac{Total\ Number\ of\ Subjects\ with\ \text{TEAEs}}{Total\ Number\ of\ Subjects}$

Exposure Adjusted IR (EAIR) = $\frac{Total\ Number\ of\ \text{TEAEs}}{Total\ Number\ of\ Infusions\ Administered\ Across\ All\ Subjects}$

Therefore the PT will be considered to meet the criterion only if both of the following are true:

(CSL112 IR-Placebo IR)x100% ≥ 1%.

$\left(\frac{CSL112\ 6g\ EAIR - Placebo\ EAIR}{Placebo\ EAIR}\right) 100\% \geq 30\%$, where Placebo EAIR > 0.

If the number of events within the placebo group is 0 (ie, Placebo EAIR = 0), then the PT will be considered to be an adverse drug reaction if (CSL112 IR-Placebo IR) ≥ 1%.

11.3.1 Suspected Adverse Drug Reactions (ADRs)

An additional summary of suspected ADRs as specified in CSL112 investigator brochure (Version V12, Section 7.5, Table 35) will be provided, sorted in descending order of frequency by PT in the CSL112 arm. PTs related to the following categories of adverse events are defined consistent with the current CSL112 investigator brochure.

- Injection and infusion site reactions
- Venipuncture and catheter site related reactions
- PTs corresponding to high level term of Headaches NEC
- PTs corresponding to high level term of Urinary Tract Infection
- Single PT of Myalgia

Supportive listings of adverse events meeting definitions of suspected ADRs will be provided.

11.3.2 Summary of Infusion Site or Injection Site Reactions

Local tolerability reactions will be analyzed based on groupings of PTs. Infusion and injection site reactions, and venipuncture and catheter site reactions had been identified as ADRs in the completed CSL112 clinical studies. A table will be provided for each grouping of terms below, which will be summarized by PT and treatment group:

- Infusion site reactions: all PTs beginning with “infusion site”
- Injection site reactions: all PTs beginning with “injection site”
- Venipuncture and catheter site reactions: all PTs beginning with “catheter site”, “puncture site”, “vascular site access”, “vessel puncture site”.

The summary table will be sorted in descending order by frequency of PT in the CSL112 arm.

11.4 Public Disclosure of Clinical Trials Requirements

To support public disclosure requirements for a clinical study, a summary of SAEs and their relationship to study treatment will be provided. These summaries will be displayed by SOC and PT and will include number and percentage of subjects for each SAE and the number of instances of each.

Additionally, a summary of only non-serious TEAEs occurring in at least 5% of the subjects in at least one treatment arm will be provided. The summary will be displayed by SOC and PT and will include number and percentage of subjects for each TEAE and the number of instances of each TEAE. It will be sorted in decreasing frequency of incidence in the CSL112 arm.

Summaries to be produced are:

- Treatment-emergent SAEs by SOC and PT
- Treatment-emergent SAEs by SOC and PT with Relationship to Study Treatment
- Non-Serious AEs experienced by more than 5% of subjects in any treatment group, by SOC and PT
- Non-Serious AEs by SOC and PT.

11.5 Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If a subject or a subject's partner becomes pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

11.6 Clinical Laboratory Evaluations

11.6.1 General Considerations for Laboratory Data

The list of planned laboratory parameters to be evaluated in this study is shown in Table 11-1.

Table 11-1 List of Planned Laboratory Parameters

Hematology	Hemoglobin	Hematocrit	WBC counts
	Total platelet count	CBC with differential	
Biochemistry	Alkaline phosphatase	ALT	AST
	TBili	Direct bilirubin	BUN
	Cholesterol [a]	LDL cholesterol [a]	HDL cholesterol [a]
	Creatinine	eGFR (calculated)	Triglycerides [a]
	Indirect bilirubin (calculated)		

- ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; cholesterol = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein; CBC = complete blood count; ALT = alanineaminotransferase; AST = Aspartate aminotransferase.
- [a] Lipid panel test results will remain blinded

With the exception of ALT and Tbili used to identify potential hepatic injury events, analysis of clinical laboratory data will be based on results from the central laboratory. Local laboratory results will be included in data listings. The definition of baseline value given in Section 8.2.5 will be applied when assessing change from baseline. The denominator in calculating any percentage will be the number of subjects with a non-missing, valid result at that time point; for shift tables, the denominator corresponds to the number of subjects with a valid result at both baseline and study visit of interest. The laboratory normal reference ranges will be provided and clinical laboratory test results outside the normal reference range will be flagged in the laboratory data listings.

When quantitative laboratory measurements reported are with qualifiers such as "< lower limit of normal" or "> upper limit of normal", the numeric portion of the laboratory result will be used for the purpose of summarizing the data; however, the actual result will be presented in data listings.

Quantitative laboratory measurements will be categorized based on a comparison with the relevant reference normal range (SI units) as follows:

- Low: Below the lower limit of the normal range
- Normal: Within the normal range
- High: Above the upper limit of the normal range

11.6.2 Analysis of Clinical Laboratory Data

The laboratory data will be summarized as described below for all parameters:

- Actual and change from baseline will be presented by scheduled study visit for quantitative values. Unscheduled assessments will be excluded.
- Analysis of shifts from baseline to worst observation will be summarized. For hemoglobin, hematocrit, and platelets, 'Low' values will be considered in determining the worst observation whereas 'High' values will be of interest for laboratory parameters including WBC, alkaline phosphatase, ALT, AST, and bilirubin (total, direct, and indirect) . Worst value determination will include scheduled and unscheduled assessments.
- Box plots of actual values and change from baseline will be presented by treatment and study visit
- The number (%) of subjects meeting the grade 3 or 4 toxicity criteria [CTCAE] for select renal and hepatic parameters as defined in Table 11-2 will be summarized.

Table 11-2 Select Renal and Hepatic Grades 3 and 4 Laboratory Abnormalities

Lab parameter	Grade 3	Grade 4
Alkaline phosphatase	> 5 - 20x ULN	> 20x ULN
ALT	> 5 - 20x ULN	> 20x ULN
AST	> 5 -20x ULN	> 20x ULN
TBili	> 3x - 10x ULN	> 10x ULN
Direct bilirubin	> 3x - 10x ULN	> 10x ULN
Indirect bilirubin	> 3x - 10x ULN	> 10x ULN
Creatinine	> 3x Baseline > 3 - 6x ULN	> 6x ULN

11.6.2.1 Renal Function:

Additional summaries of serum creatinine and eGFR (for derivation, see Table 8-1) will be presented to characterize the effect of CSL112 on renal function. The tables listed below will be generated for all subjects as well by subgroups defined on the basis of renal function categories and by time delay between contrast administration and IP administration, both alone and in combination. The three renal function subgroups are defined as normal (eGFR ≥90 mL/min/1.73 m^2), mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2), and moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m2). The three subgroups for time delay between administration of contrast and IP are defined as <24 hours, ≥24 hours-<48 hours and ≥48 hours. Thus, there are a total of nine subgroups:

- Categories of absolute change from baseline in serum creatinine defined as ≤baseline value, >0 to <27, ≥27 to ≤44, >44 -µmol/L (> 0 to < 0.3, ≥0.3 to ≤ 0.5, and >0.5 mg/dL); number (%) of subjects in each category will be presented. Categorization of change from baseline in serum creatinine will be based SI units (µmol/L) while conventional units are given for descriptive purposes.
- Number (%) of subjects achieving a threshold rise of ≥ 27 µmol/L (0.3 mg/dL) one or more occasions as well as on two or more consecutive occasions will be presented
- Categories of increase in serum creatinine including ≥1.5 x baseline, ≥ 2 x baseline, ≥ 3 x baseline

- Number (%) of subjects with raw serum creatinine value ≥ 354 µmol/L(4.0 mg/dL)
- Decreases in eGFR of 25% or more from baseline at any time
- Supportive data listings of individual subject data meeting the above-mentioned criteria will be generated
- Data listings including subjects with one or more values outside the reference range will be produced

Assessment of Drug-Biologic Interactions:

Incidence of elevations in serum creatinine defined as a change from baseline ≥ 27 ~~26.53~~ µmol/L (0.3 mg/dL) will be summarized by concomitant use of ACEI or ARBs where concomitant is defined for this summary as any time during the active treatment period.

11.6.2.2 Hepatic function:

Liver Dysfunction:

The number (%) of subjects experiencing concomitant elevations in ALT > 3 x ULN and Tbili > 2 x ULN or ALT > 5 x ULN will be determined. Incidence rates along with 95% CI s [Newcombe, 1998] will be provided. A plot of TBili versus ALT will be generated.

Assessment of Drug-Biologic Interaction:

The impact on liver function due to potential interactions between CSL112 and statins and PCS K9 inhibitors will be investigated by summarizing the incidence of elevations (ALT > 3 x ULN and Tbili > 2 x ULN or ALT > 5 x ULN) in ALT and TBili in the following subgroups:

- No statins and no PCSK9i
- No statins and any PCSK9i
- Low or moderate potency statins and no PCSK9i
- Low or moderate potency statins and any PCSK9i
- High potency statins and no PCSK9i
- High potency statins and any PCSK9i

11.7 Other Safety Measures

11.7.1 Evaluation of Immunogenic Potential

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

11.7.2 Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Pulse (bpm)
- Weight (kg)

The following summaries will be provided:

- Actual and change from baseline by visit
- Incidence of treatment emergent markedly abnormal vital signs will be derived according to the rules defined in Table 8-2.

If a subject has a shift from baseline to both low and high, then the subject will be counted in both the low and the high categories.

- Incidence of subjects meeting markedly abnormal values
- Listing of all Vital Signs data and of subjects meeting markedly abnormal criteria
- For SBP, DBP and pulse, the change from baseline at each visit and by treatment group will be presented visually using box plots.

11.7.3 Physical Examination

A brief, directed physical examination focusing on pulmonary and CV exam, will be performed at screening and any clinically significant changes occurring between screening and Visit 8/Day 90, including drug hypersensitivity findings will be documented in the eCRF as an AE. Accordingly, no summary tables or listings will be produced.

11.7.4 Parvovirus Testing

Samples will be collected from all randomized subjects at Visit 2 (Day 1; before infusion 1) and Visit 6 (Day 29). Nucleic acid testing and serology (parvovirus B19) will be performed using complete samples (at Day 1 and 29) from approximately 300 randomly selected subjects (approximately 150 CSL112 and 150 placebo) to evaluate changes from baseline (ie, evidence of seroconversion or infection) for parvovirus B19.

Central lab results for Parvo 19 antibodies IgG and IgM will be categorized as negative, equivocal, or positive. Parvo B19 DNA will be reported as detected/not detected. A shift analysis of change from baseline to Visit 6 will be presented.

A subject data listing including central laboratory results for human parvovirus B19, Parvovirus B19 IgG antibody and Parvovirus B19 IgM antibody will be provided.

12 PK Analyses

PK sub-study will be performed to conduct a population PK analysis. Accordingly, blood samples will be drawn at pre-infusion 1, end of infusion 1, and end of infusion 4. The concentrations of apoA-I and PC will be assayed. The following PK endpoints are planned:

- Baseline-corrected apoA-I concentrations [concentration at end of infusion 1 or 4 minus baseline]
- Baseline-corrected plasma PC concentrations [concentration at end of infusion 1 or 4 minus baseline]
- Concentration in plasma at the end of infusion for apoA-I and PC
- Accumulation ratio for apoA-I and PC [Baseline corrected concentration at end of infusion 4 / baseline corrected concentration at end of infusion 1]

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

13 PD Analyses

The following pharmacodynamic endpoints are included to support the exploratory objective assessed in the PD sub-study:

a. Total cholesterol efflux

b. ABCA1-dependent efflux

c. ABCA1-independent efflux

Blood samples for pharmacodynamic assessments will be drawn at the same as time points as pharmacokinetic draws. For each of the above endpoints, the change from baseline will be derived for each parameter and a two sample t-test will be used to compare the two treatment arms. Geometric mean ratios of each PD parameter at the end of infusions 1 and 4 relative to baseline will be summarized.

14 References

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15 Appendices

15.1 Description of Win Ratio Methodology

The unmatched win ratio method [Pocock et al, 2012] is employed to analyze the composite endpoint of recurrent hospitalizations for coronary, cerebral, or peripheral ischemia or all-cause death over 90 days by allowing for clinical priorities; ie, that death is a more important outcome than hospitalization.

In the unmatched win ratio approach, every subject on CSL112 is compared with every subject on placebo, each time noting who 'won'. If N_t and N_c are the total number of subjects assigned to CSL112 (test treatment) and placebo (control treatment) then a total of N_t x N_c paired comparisons are made. Each pair is classified into one of five categories (a), (b), (c), (d), or (e) as shown below:

a. CSL112 subject experienced death first [CSL112 loser]

b. Placebo subject experienced death first [CSL112 winner]

c. CSL112 had a greater number of hospitalizations [CSL112 loser]

d. Placebo subject had a greater number of hospitalizations [CSL112 winner]

e. None of the above (a tie)

For each pair, CSL112 is a 'winner' or 'loser' according to which subject experienced death first. If no death occurred by Day 90, then whether CSL112 is labelled a 'winner' or 'loser' depends on which subject had more hospitalizations. Otherwise, the two treatments are tied. The number of matched pairs in categories a, b, c, d, and e are summarized by N_a, N_b, N_c, N_d, and N_e, respectively. The number of winners and losers on CSL112 are defined as $N_w = N_b + N_d$ and $N_L = N_a + N_c$ with $Rw = N_w / N_L$ defined as the win ratio.

The derivation of a 1-sided *P* value for the win ratio is given below:

Let total sample size, $N = N_t + N_c$

For each paired comparison *ij* where Treatment for subject i is not equal to Treatment for subject j, let $U_{ij} = +1, -1$, or 0 according to whether patient i is the winner, loser or they tied. Then for patient i, define $U_i = \Sigma u_{ij}$ where U_i is a positive integer if patient i wins more than loses. Further define $T = \Sigma U_i D_i$ where $D_i = 1$ if patient i is assigned to CSL112 and 0

otherwise. The variance of T is given by V where V = $\left(\frac{N_t N_c}{N\,(N-1)} * \sum U_i^2\right)$ under the null hypothesis of no true difference between CSL112 and placebo. Then $z = \frac{T}{\sqrt{V}}$ is a standardized normal deviate, and the one-sided p-value is obtained from a cumulative normal distribution as 1 - prob ($Z \leq z$). Corresponding SAS code is given as 1 – CDF ('NORMAL', z).

A win ratio (CSL112: Placebo) > 1 is indicative of superiority of treatment with CSL112 over placebo.

15.2 Analysis of Questionnaire EQ-5D-3L

The EQ-5D-3L is a patient self-assessment of five dimensions of health-related quality of life (HRQOL): mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each dimension is measured on a 3-point scale (no problem, some problems, and extreme problems) where a higher score corresponds to a worse health state. The score on each dimension is analyzed separately. In addition, patient's self-assessment on all five dimensions assigns each patient to one of 243 possible health states (ie, from 11111 to 33333 where each digit corresponds to one of the five dimensions and each number corresponds to the rating on each dimension). Each of these 243 possible health states is then mapped to a specific utility score which will be analyzed as a continuous score as well as be employed in a cost-effectiveness analysis. The tariff to be used for the mapping is given by [Dolan and Roberts, 2002]. The UK-specific scoring algorithm will be utilized in the analysis and is illustrated with the following example: a subject provides the following responses: Mobility=No problems, Self-care=No problems, Usual Activities=Moderate problems, Pain/Discomfort=Moderate problems, Anxiety/Depression=Extreme problems. Therefore, the response sequence is 11223.

The utility score for the subject with example sequence 11223 = 0.255 is calculated as shown in Table 15–1.

Table 15-1 EQ-5D-3L Scoring Algorithm

Domain Score	Tariff	Example Subject with Sequence 11223 Utility Score = -0.255	
Full health (11111)	1.000		1.000
Constant term (for any dysfunctional state):	-0.081		-0.081
Mobility level 1:	0	√	0
Mobility level 2:	-0.069		
Mobility level 3:	-0.314		
Self-care level 1:	0	√	0
Self-care level 2:	-0.104		
Self-care level 3:	-0.214		
Usual activities 1:	0		
Usual activities 2:	-0.036	√	-0.036
Usual activities 3:	-0.094		
Pain/discomfort 1:	**0**		
Pain/discomfort 2:	-0.123	√	-0.123
Pain/discomfort 3:	-0.386		
Anxiety/depression 1:	0		
Anxiety/depression 2:	-0.071		
Anxiety depression 3:	-0.236	√	-0.236
At least one domain at 3 (N3):	-0.269		-0.269

Any missing values which are coded as '9' will be set to missing (and hence no health state value will be calculated). Ambiguous values (eg, 2 boxes ticked for a single dimension) will be treated as missing values. If 1 or more domains are missing the HSV will not be calculated

The EQ VAS (visual analogue scale) is a continuous 100 point integer scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine). Missing values will be recorded as '999' but will be replaced by a missing value for all analyses. Ambiguous values (e.g., the line crosses the VAS twice) will be treated as missing values.

Analysis of the five dimension scores:

Each of the five dimension scores will be descriptively summarized and analyzed separately. For each treatment, shift tables will be employed indicating the number of patients whose score falls into a grid defined by the baseline value on one axis and the post-treatment value on the other axis. To compare treatments on each dimension, the number of patients with improvement, no change and worsening from baseline to the post-treatment value will be

analyzed using a chi-square test for a 2 x 3 contingency table with ordered categories of response.

Analysis of the EQ VAS and Utility Score:

Both the EQ VAS and the utility score are continuous response variables describing the patient's self-assessment of their health status at baseline and post-treatment. Descriptive statistics including the mean, median, SD, minimum and maximum will be provided at baseline, post-treatment and for the change from baseline. The difference between baseline and post-treatment will be compared between treatments employing an analysis of variance model (ANOVA) including terms for treatment, each of the stratification factors (region, type of MI (STEMI vs NSTEMI) and management of MI (PCI vs. medical management)).

15.3 Selected Regions and Countries for Study Participation

Table 15-2 Estimated Regional Subject Allocation

Region	Country	Number of Sites	Number (%) Randomized
NA	Canada, United States	300	4375 (25%)
LA	Argentina, Brazil, Chile, Colombia , Mexico	100	1750 (10%)
WE	Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, Turkey, United Kingdom	270	3500 (20%)
CEE	Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, Ukraine	230	6125 (35%)
AP	Australia, Hong Kong, Malaysia, New Zealand, Singapore, South Korea, Taiwan, Thailand, Japan	100	1750 (10%)

NA = North America, LA = Latin America, WE = Western Europe, CEE = Central and Eastern Europe, and AP = Asia Pacific

15.4 Interpretation of Subgroup Analyses

On January 31, 2019, the European Medicines Agency (EMA) published *Guideline on the investigation of subgroups in confirmatory clinical trials*, which came into effect on August 1, 2019. The guideline states that assessment of relevant subgroups is an important step to support the conclusion that the treatment effect applies to the potentially heterogeneous population of a trial. Consideration of multiple subgroups increases the probability of false positives, i.e. conclusions that the treatment effect in a subgroup differs from that in the rest of the primary trial population, when in truth it does not. False negative conclusions, when it is not detected that the treatment effect in a subgroup truly does differ from that in the rest of the primary trial population, are also possible. The possibility of false positives and false negatives, however, does not justify ignoring or dismissing differential treatment effects which are observed. It is crucial to investigate the underlying hypothesis that effects across different subgroups are consistent with the overall outcome of the trial, and it is not acceptable to assume that treatment effect is consistent across important subgroups without further investigation and discussion.

Within this study, factors defining subgroups are classified into the following two categories:

1. Key Subgroups: A factor for which there is some biological plausibility or external evidence such that an inconsistent response might be observed. This category includes factors used to stratify the randomization, as well as other subject characteristics.

2. Exploratory Subgroups: A factor for which there is good argumentation why consistency of response to treatment is plausible.

The assessment of subgroups should start with subgroups defined by the factors used to stratify randomization and then proceed with subgroups defined by factors where there is a priori suspicion that they may influence the treatment effect. Once these have been fully evaluated, further assessment of relevant subgroups should be undertaken for factors for which there is no a priori rationale that the treatment effect should be modulated. Subgroups should be pre-specified and categorized a priori, i.e. before trial results are known.

Factors defining key subgroups (i.e. those belonging to category 1 above) are listed in the table below:

Factor Defining Key Subgroups	Rationale for Designation as "Key"
Index MI type (STEMI vs NSTEMI)	Stratification factors
Management of the index MI (percutaneous coronary intervention versus medically managed)	
Region (North America, Latin America, Western Europe, Central and Eastern Europe, or Asia Pacific)	

Assessment of whether subgroups are expected to show differential treatment effects is based on the mechanism of action of CSL112, which enhances cholesterol efflux from macrophages within atherosclerotic plaque. All subjects enrolled in the trial, under both the original protocol and Amendment 1, are required to have evidence of multivessel atherosclerotic coronary artery disease. Thus, in general, consistent treatment effects are expected across trial subgroups.

The stratification factors may be prognostic of outcome. However, based on the mechanism of action of CSL112, no differential response to treatment is expected among subgroups defined by these factors.

One factor defining subgroups meriting special consideration is enrollment before or after Protocol Amendment 1. According to the original protocol, a subject was required to have at least one of the following established risk factors: age ≥ 65 years, prior history of MI, on pharmacological treatment for diabetes mellitus, or PAD. In protocol amendment 1, the entry criteria were modified to enhance the primary endpoint event rate, because the previously observed blinded aggregate event rate was lower than expected. The modified risk factor criterion requires subjects to be on pharmacological treatment for diabetes mellitus or have at least two of the other risk factors: age ≥ 65 years, prior history of MI, or PAD. Subgroups reflecting the modified enrichment criteria, or not, will be examined in an exploratory fashion. Consistency of response to treatment across these two subgroups is expected based on the mechanism of action of CSL112. In addition, the individual risk factors themselves being utilized in the original protocol and amendment 1 are the same. However, in protocol amendment 1, the modification will lead to the enrollment of subjects who are expected to have a higher risk of experiencing an early recurrent cardiovascular event. Finally, the two subgroups will be similar in the standard of care treatments that they will receive, in particular, the utilization of percutaneous coronary revascularization, and medications such as dual antiplatelet therapy, and statins. Hence, it is only the severity of disease, and thus the

magnitude of the event rate, which is expected to differ. No differential response to treatment is expected between the two subgroups; therefore, these subgroups belong to category 2 above and are considered exploratory.

The subgroups which will be assessed are defined in Section 10.1.2, along with descriptions of statistical methodology which will be used for subgroup analyses of the primary efficacy endpoint, defined as the time to first occurrence of any component of the composite MACE, ie, CV death, MI, or stroke, from the time of randomization through 90 days. There is no pharmacological rationale or clinical evidence to indicate that treatment effect might differ among these subgroups. Except for the subgroups defined by stratification factors, these subgroups belong to category 2, described above, and will be considered exploratory.

The following displays will be provided for all subgroup analyses of the primary endpoint:

- A summary for each level of each factor defining a subgroup, including the number at risk, number (%) with events, hazard ratio and 95% CI,
- A two-sided Wald p-value for the interaction term,
- A forest plot including each level of each factor defining a subgroup with hazard ratio and 95% CI

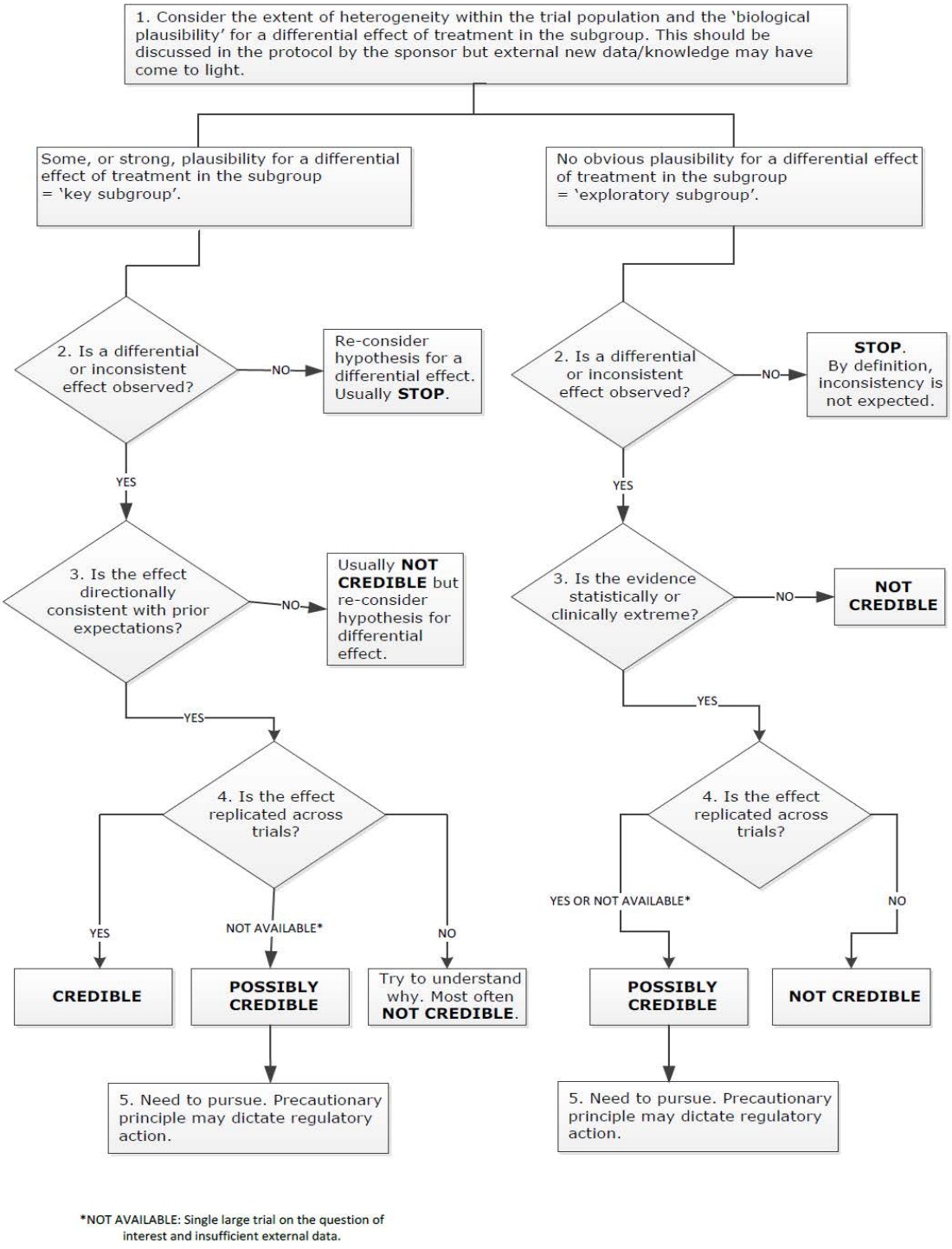
The EMA guideline states that no formal rule for the interpretation of subgroup findings presented in a Forest plot, that is both sensitive to detect inconsistency in treatment effects and specific to avoid false-positive findings, is available. Inconsistencies in treatment effect of primary concern are those which are qualitative, i.e. those for which the treatment effect is directionally different in the subgroup. The guideline presents a flowchart for establishing "credibility". The flowchart for establishing credibility when considering consistency is presented below. Since the CSL112 development program includes a single pivotal outcomes trial supporting registration, and no relevant external data exists, there is no possibility of replicating subgroup analysis results to ascertain consistency across trials. An assessment of credibility will consider the estimate and precision of the overall effect, the estimate and confidence interval of the subgroups, the p-value for the test of interaction, and the clinical relevance. Inconsistencies in treatment effect of primary concern are those which are qualitative, ie, those for which the treatment effect is directionally different in the subgroup.

In the case where there is some or strong biological plausibility for a differential treatment effect in the subgroup, if a differential or inconsistent effect is observed, and the effect is

directionally consistent with prior expectations, then the differential treatment effect may be considered credible, and hence subject to further sponsor evaluation and regulatory consideration.

In the case where there is no biological plausibility for a differential treatment effect in the subgroup, i.e. for an "exploratory subgroup", but a differential or inconsistent effect is observed, it must be assessed whether the evidence is statistically or clinically extreme. If the evidence is not statistically or clinically extreme, the differential treatment effect will be considered not credible. Further details are provided in the flowchart below [Source: EMA Guideline on the investigation of subgroups in confirmatory clinical trials (31 Jan 2019)]:

Flowchart for establishing 'credibility' when considering 'consistency'



15.5 SAS Code

PROC FREQ (NEWCOMBE WILSON):

```
PROC FREQ DATA=<xxx>;
        TABLE treatment*<endpoint> / RISKDIFF (CL=(newcombe) column=2) OUT=<yyy>;
RUN;
```

Cox Proportional Hazards Regression Model:

PROC PHREG DATA=<xxx>;

```
CLASS TREATMENT MI_TYPE MI_MANAGEMENT REGION PERIPHERAL_ARTERY_DISEASE DIABETES MI_HISTORY;
MODEL <TIME>*<CENSORING>(1) = TREATMENT MI_TYPE MI_MANAGEMENT REGION AGE PERIPHERAL_ARTERY_DISEASE DIABETES
   MI_HISTORY MI_TYPE*MI_MANAGEMENT;
RUN;
```

Negative Binomial Regression Model using PROC GENMOD:

```
PROC GENMOD DATA=;
Class TREATMENT MI_TYPE MI_MANAGEMENT REGION PERIPHERAL_ARTERY_DISEASE DIABETES MI_HISTORY;
Model <endpoint> = TREATMENT MI_TYPE MI_MANAGEMENT REGION AGE PERIPHERAL_ARTERY_DISEASE DIABETES MI_HISTORY
MI_TYPE*MI_MANAGEMENT/ link=log distbn=nb offset=logt;
Run;
```

Imputation of Missing Baseline Covariates/Risk Factors:

```
PROC MI data= NIMPUTE=1 OUT=;
        CLASS PERIPHERAL_ARTERY_DISEASE DIABETES MI_HISTORY;
        VAR MI_TYPE MI_MANAGEMENT REGION AGE PERIPHERAL_ARTERY_DISEASE DIABETES MI_HISTORY;
        FCS LOGISTIC(PERIPHERAL_ARTERY_DISEASE DIABETES MI_HISTORY / LINK=GLOGIT);
RUN;
```

Tipping Point Analysis:

```
PROC PHREG DATA= ;
        CLASS MI_TYPE MI_MANAGEMENT REGION PERIPHERAL_ARTERY_DISEASE DIABETES MI_HISTORY;
        MODEL AVAL*NCNSR(1)= AGE MI_TYPE MI_MANAGEMENT REGION AGE PERIPHERAL_ARTERY_DISEASE DIABETES MI_HISTORY
        MI_TYPE*MI_MANAGEMENT;
        BAYES SEED=1234 PIECEWISE=HAZARD (INTERVAL=(10 30 50) PRIOR=GAMMA) NBI=2000 THINNING=50 NMC=2500;
        BY TRT;
RUN;
```

One-sided *P* value will be obtained as follows:

The Wald *P* value from the Cox/negative binomial regression model will be transformed to a 1-sided *P* values follows: if the estimated hazard/risk ratio for treatment effect is less than 1, the resulting *P* value will be set to 0.5*Wald *P* value; otherwise, if the estimated hazard/risk ratio is greater than 1 then the result *P* value will be set to 1-0.5*Wald *P* value.

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Signed By	Date (GMT)
PPD	12-Jan-2024 16:00:01
Approved-Biostatistician Lead Approval	
PPD	14-Jan-2024 20:07:11
Approved-Clinical Development Physician Approval	

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