STATISTICAL ANALYSIS PLAN (SAP)

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

Investigational Medicinal Product: CSL112

Protocol Number: CSL112_2001

Version: 1.0 Final

Version Date: 03-AUG-2017

Sponsor: CSL Behring

Signature page

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1 Modification History

Version	Effective Date	Author of Modification	Reason for Change
0.1 (Draft)	10NOV2016	PPD CSL Statisitician	N/A – First Draft Version.
0.2 (Draft)	26DEC2016	PPD Statistician	First Draft for Review.
0.3 (Draft)	03JAN2017	PPD Statistician	Updates inline with Draft Shell Creation.
1.0 (Draft)	22FEB2017	PPD Statistician	Updates based on First Round of CSL Feedback.
1.1 (Draft)	07MAR2017	PPD Statistician	Updates based on v1.0 Feedback from CSL Biostatistics.
1.2 (Draft)	25APR2017	PPD Statistician	Updates incorporated for production of Dry Run 1.
2.0 (Draft)	22MAY2017	PPD Statistician	Updates based on Feedback v.1.1 and the Dry Run 1 from CSL .
2.1 (Draft)	20JUN2017	PPD Statistician	Updates incorporated for production of Dry Run 2.
2.2 (Draft)	19JUL2017	PPD Statistician	Updates based on Feedback v.2.1 and the Dry Run 2 from CSL .
2.3(Draft)	03AUG2017	PPD Statistician	Minor updates in build up to Database Lock.
1.0 (Final)	03AUG2017	PPD Statistician	Rounded for Final Versioning and Signatures.

2 List of Abbreviations

ABCA1	ATP-Binding Cassette Transporter 1
aCS	Abnormal, Clinically Significant
AE	Adverse Event
AESI	Adverse Events of Special Interest
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
aNCS	Abnormal, Not Clinically Significant
ApoA-I	Apolipoprotein A-I
CCI	[redacted]
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CV	Cardiovascular
CV %	Coefficient of Variation
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
FDA	Food and Drug Administration
FMC	First Medical Contact
Gmean	Geometric Mean

GSD	Geometric Standard Deviation
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
CCI [redacted]	[redacted]
IND	Investigational New Drug
IP	Investigational Product
ISO	International Organization for Standardization
ITT	Intent–to-Treat
IV	Intravenous
IRT	Interactive Response Technology
KDIGO	Kidney Disease Improving Global Outcomes
LDH	Lactate Dehydrogenase
CCI [redacted]	[redacted]
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
mRNA	Messenger Ribonucleic Acid
n	Number of Observations
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
NSTEMI	Non-ST Segment Elevation Myocardial Infarction
CCI [redacted]	[redacted]
PC	Phosphatidylcholine
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
QTcB	Bazett's QT correction
QTcF	Fridericia's QT correction
R_A	Accumulation Ratio
RI	Renal Impairment

SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCR	All Subjects Screened
SD	Standard Deviation
SI	International System
SMQ	Standard MedDRA Query
SOC	System Organ Class
STEMI	ST Segment Elevation Myocardial Infarction
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings and Figures
ULN	Upper Limit of Normal
URS	User Requirements Specification
USA	United States of America
WBC	White Blood Cells
WHODD	World Health Organization Drug Dictionary

3 Purpose

This statistical analysis plan (SAP) provides a detailed and complete description for the final analysis of the study CSL112_2001 to support the Clinical Study Report (CSR). 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. It is based upon the following study document:

- Study Protocol Amendment 1 (dated 6th June 2016)
- Country-specific Clinical Protocol for the United States of America (USA) (dated 6th June 2016)

Selected pharmacokinetic (PK) CCI [redacted] analysis plans will be provided as separate documents.

All decisions regarding the final analysis of the study results, as defined in this SAP document, have been agreed prior to Database Lock of the study data.

4 Study Design

4.1 Study Design

This is a phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and tolerability of up to 4 weekly intravenous (IV) administrations of CSL112 6g compared with Placebo in subjects with moderate renal impairment (RI) and acute myocardial infarction (AMI).

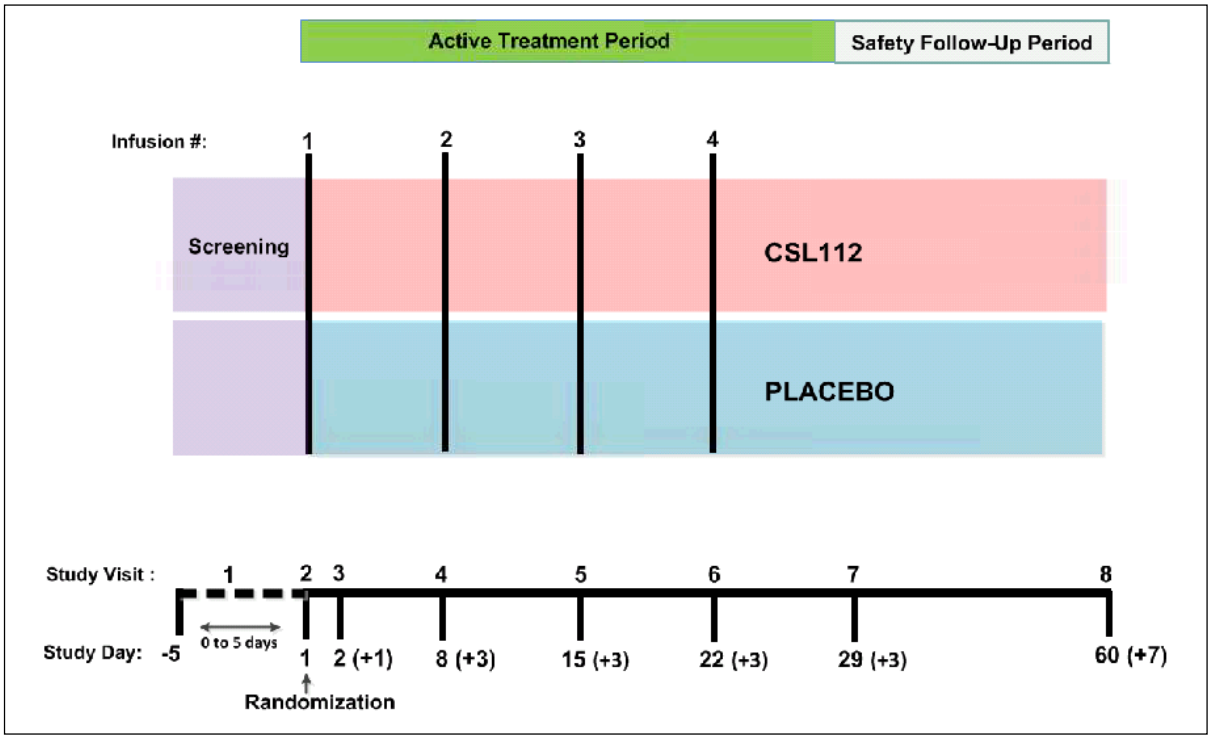
The study will consist of a screening period and 2 study periods: an Active Treatment Period during which subjects will receive 4 IV infusions of investigational product (IP) over approximately 22 days and a Safety Follow-up Period, beginning approximately 7 days after the last infusion and lasting approximately 30 days. The Active Treatment Period and the Safety Follow-up Period are defined in Sections 4.1.2 and 4.1.3 respectively. The final analysis to support the CSR will be performed after study completion.

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

The main study will enroll approximately 81 subjects who will be randomly assigned in a 2:1 ratio to receive infusions of CSL112 6g (54 subjects) versus placebo (27 subjects) to evaluate safety and tolerability. Randomization will be stratified by estimated Glomerular Filtration Rate (eGFR) (30 - <45 mL/min/1.73 m^2 or 45 - <60 mL/min/1.73 m^2, as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [Levey et al, 2009; Stevens et al, 2010]) and by medical history of diabetes requiring current treatment with any anti-diabetic medication (yes or no).

To ensure at least one-third of randomized subjects have eGFR between 30 - <45 mL/min/1.73 m^2, randomization of subjects with eGFR between 45 - <60 mL/min/1.73 m^2 will be restricted to no more than 54 subjects. CCI [redacted]

Figure 4-1: Study Overview



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

4.1.1 Screening Period

The Screening Period is defined as the period of time leading up to and including randomization and expected to last for approximately 5 days. Randomization must occur within 5 days of first medical contact (FMC) for the index AMI.

Note that at the beginning of the study, sites in the United States were required to ensure that prior to any first infusion, subjects were clinically stable at least 48 hours after the index MI, resulting in a Screening Period of 7 days. However the DSMB made the recommendation to permit earlier administration of the first infusion bringing the Screening Period for sites in the United States inline with sites in the rest of the world (5 Days). Further details are given in Section 5 regarding the DSMB recommendation.

Note that Screening and randomization of subjects may occur on the same day (Study Day 1 of the Active Treatment Period) provided that the minimum time for assessment of renal function stability is adhered to before administration of the first infusion of IP. Refer to Section 8.2.1.2 of the study protocol (Amendment 1, 6th June 2016) for further details.

4.1.2 Active Treatment Period

The Active Treatment Period is expected to last for approximately 28 days and begins at the time of a subject's first infusion. The end of the Active Treatment Period occurs at the end of the day of Visit 7 (Study Day 29).

If the Visit 7 assessment was not performed, then the end of the Active Treatment Period is the date of the subject's last administration of study medication + 10 (7+3) calendar days. If an event occurred at any time on the 10th day after the day of the last administration, this would be deemed to be within the Active Treatment Period.

4.1.3 Safety Follow-Up Period

The Safety Follow-up Period is expected to last for approximately 30 days and will begin the day after the end of the Active Treatment Period. Subjects will return to the study clinic at Visit 8 (Study Day 60) for assessment of adverse events (AEs) and other safety procedures.

4.2 Objectives and Endpoints

Objectives	Endpoints
Primary	
The primary objective of this study is to assess the renal safety of CSL112 in subjects with moderate RI and AMI after administration of up to 4 weekly infusions of CSL112.	The renal safety profile of CSL112 in subjects with moderate RI and AMI who receive up to 4 weekly administrations of CSL112 will be assessed by co-primary endpoints of the incidences of treatment-emergent (1) renal serious adverse events (SAEs) as defined below, and (2) Acute kidney injury (AKI), defined as an absolute increase in serum creatinine (central laboratory) from baseline ≥ 0.3 mg/dL (26.5

Objectives	Endpoints
	µmol/L) during the Active Treatment Period that is sustained upon repeat measurement by the central laboratory no earlier than 24 hours after the elevated value. If no repeat value is obtained [due, for example, to loss to follow-up or protocol violation], a single serum creatinine value that is increased from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period would also fulfil the definition of AKI. Treatment-emergent is defined as occurring at or after the start of the first infusion. Baseline for determination of AKI is defined as the pre-infusion central laboratory serum creatinine level on Study Day 1 (Visit 2). A renal SAE is defined as any SAE with a Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) included in the Acute Renal Failure **narrow** Standard MedDRA Query (SMQ) or a PT of • Renal Tubular Necrosis, • Renal Cortical Necrosis, • Renal Necrosis, or • Renal Papillary Necrosis. Incidence rates will be based on the number of subjects with at least 1 occurrence of the event of interest; that is, a subject with 2 treatment-emergent renal SAEs or 2 instances of AKI will be counted once.
Secondary	
The secondary objectives of the study are: 1. To further characterize the safety and tolerability of CSL112 in subjects with moderate RI and AMI. 2. To characterize the PK of CSL112 after multiple dose administration in subjects with moderate RI and AMI.	Secondary safety and tolerability endpoints include: 1. The occurrence of any treatment-emergent adverse event (TEAE) throughout the study. 2. The occurrence of treatment-emergent adverse drug reactions or suspected

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

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

Objectives	Endpoints
	7. The occurrence of binding antibodies specific to apoA-I and/or CSL112.
	Secondary PK Endpoints 1. Baseline (ie, pre-infusion on Study Day 1)-corrected plasma apoA-I concentrations 2. Baseline-corrected plasma PC concentrations 3. Concentration in plasma at End-of-Infusion for apoA-I and PC 4. Accumulation ratio (R_A) for apoA-I and PC
CCI	

[a] This is a correction from the original Protocol text, which specified indirect bilirubin was to be used for subjects with a history of Gilbert's Syndrome, see Section 5.

4.2.1 Primary Study Hypotheses

There are no statistical hypothesis tests for this study.

4.3 Study Treatments

Subjects receive four, 2-hour IV infusions of IP (CSL112 6g or Placebo), 7 to 10 days apart, during a 4-week Active Treatment Period, with all 4 infusions administered within 30 days from Study Day 1 (Visit 2).

4.4 Schedule of Assessments

The schedules of assessments for the study can be found in the synopsis of the study protocol.

4.5 Randomization Procedures and Blinding

Eligible subjects were to be randomized in a 2:1 ratio to receive active treatment versus placebo by means of interactive response technology (IRT). Randomization was to be stratified by eGFR (30 to < 45 mL/min/1.73m^2 or 45 to < 60 mL/min/1.73m^2) and by medical history of diabetes requiring current treatment with any anti-diabetic medication (yes or no). This randomization scheme results in 4 different strata.

- 30 - <45 mL/min/1.73 m^2 with medical history of diabetes requiring current treatment with any anti-diabetic medication.
- 30 - <45 mL/min/1.73 m^2 without medical history of diabetes requiring current treatment with any anti-diabetic medication.
- 45 - <60 mL/min/1.73 m^2 with medical history of diabetes requiring current treatment with any anti-diabetic medication.
- 45 - <60 mL/min/1.73 m^2 without medical history of diabetes requiring current treatment with any anti-diabetic medication.

The eGFR values were to be calculated by the IRT using the CKD-EPI equation and local laboratory values at Visit 2 (Study Day 1). The IRT system then assigned the appropriate study treatment to each subject within each stratum.

The IRT used centralized randomization and fixed-size blocks: to ensure the study blind was maintained, a CSL statistician/delegate not directly involved in the analysis of study results was to prepare the study randomization code. The unblinded CSL statistician/delegate was to keep the randomization code on file.

To ensure adequate numbers of randomized subjects with eGFR between 30 - <45 mL/min/1.73 m^2, randomization of subjects with eGFR between 45 - <60 mL/min/1.73 m^2 was to be restricted to no more than 54 subjects.

4.5.1 Derived Stratification

For the purpose of Safety analyses, stratification will be derived based on data as reported within the database. The eGFR values will be calculated using the Visit 2 (Day 1, Before Infusion) serum creatinine values from the Central Laboratory, whilst the medical history of diabetes requiring current treatment with any anti-diabetic medication will be assigned as recorded on the medical history page of the CRF.

No imputation will be performed in the event that a subject has a missing value for the central laboratory serum creatinine.

4.6 Determination of the Sample Size

No formal sample size calculations were performed. The sample size for this study was planned to meet regulatory considerations for treatment-emergent renal event characterization; it was not powered for statistical testing of the co-primary endpoints.

With a sample size of 81 (54 CSL112 6g: 27 Placebo), the study will detect (at least one observed occurance) with 80% probability, a treatment-emergent event with a true incidence of 3% in the active group and 2% overall.

4.7 Planned Interim Analyses and Reviews

4.7.1 Interim Analyses Other Than Sample Size Re-estimation

No formal interim analyses are planned for this study.

4.7.2 Interim Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

4.7.3 Data Safety Monitoring Board Reviews

An external program-level DSMB will independently evaluate safety data to assess whether a safety signal has emerged that would warrant a change in the conduct of the study. The DSMB will also review all trial data if one or more criteria of the study level stopping rules are met. The role of the DSMB and the data review schedules are described in detail in the protocol and DSMB charter. The DSMB could recommend a change to the protocol to ameliorate any safety concerns, as specified in the program-level DSMB charter.

5 Changes in the Conduct of Planned Analyses

Section 2.2.2 of (and then throughout) the protocol incorrectly specifies the use of Indirect Bilirubin as replacement for Total Bilirubin, for subjects with a history of Gilbert's syndrome when assessing Bilirubin related secondary endpoints. This has been correctly amended in this SAP to use Direct Bilirubin.

On 13th February 2017 after reviewing the available data of approximately 35% of subjects who had received two infusions of investigational product and had pre-infusion safety data available prior to the third infusion at Visit 5, the DSMB recommended to reduce the minimum time between IV contrast and the first assessment for renal stability and dosing in the United States from 48 hours to at least 12 hours.

For subjects who had not undergone angiography with IV contrast, the first infusion would now occur no earlier than 12 hours after the subject is considered to be clinically stable after the index Myocardial Infarction (MI). As a result of this recommendation, and as per the adaptive language in the country specific USA protocol, the duration of screening was also reduced so that the screening period up to and including randomization must occur within 5 days of FMC for the index MI (reduced from 7 days).

After this recommendation, the duration of screening and the minimum time from IV contrast to first dose (or minimum time from FMC to first dose if angiography not performed) was harmonized globally.

6 Study Analysis Populations

6.1 All Subjects Screened [SCR] Population

The all subjects screened (SCR) population will consist of all subjects who provided written informed consent to undergo study screening procedures.

6.2 Intent-to-Treat [ITT] Population

The Intent-to-Treat (ITT) population will consist of all subjects in the SCR population who were randomized to 1 of the 2 treatment groups. Analyses based on this population will use the treatment to which the subject was randomized and the stratification assigned by the IRT, regardless of the treatment actually received or the true stratum to which a subject belongs. Any subject who is allocated a treatment randomization number will be considered to have been randomized.

6.3 Safety [SAF] Population

The Safety (SAF) population will consist of all subjects in the ITT population who receive at least a partial dose of IP. Analyses based on this population will use the actual treatment received and the derived stratum (See Section 4.5.1) to which a subject belongs, regardless of the treatment and stratum assigned by the IRT.

In cases where a subject receives both CSL112 6g and Placebo, the actual treatment received will be considered to be CSL112 6g.

The SAF population will be used in the analysis of all safety endpoints, including the co-primary endpoints.

6.4 Pharmacokinetic [PK] Population

The PK population will consist of all subjects in the SAF population who have at least one measurable plasma concentration of apoA-I or PC.

For displays based on the PK population, subjects will be classified according to actual treatment received and the derived stratum (See Section 4.5.1) to which they belong.

6.5 CCI

CCI

[redacted]

6.6 CCI

CCI

[redacted]

7 General Considerations

Analysis datasets will be created according to the Clinical Data Interchange Standards Consortium (CDISC) standards, and data will be displayed according to reporting standards in this SAP and the tables, listings and figures (TLF) shells.

SAS version 9.4 or higher will be used to perform all data analyses and to generate the TLFs.

Continuous variables will be summarized in terms of the number of observations (n), mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum, and maximum. Additional descriptive statistics (eg, the 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 have the specific descriptive statistics required identified with the analysis in the applicable SAP section.

All listings will include subject number and treatment group. The laboratory normal reference ranges will be provided and clinical laboratory test results outside the normal reference range will be flagged as abnormal in the laboratory data listings.

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 whole years. The SD of age will then be reported to 2 decimal places. Descriptive percentages and proportions will be displayed to one decimal place. Durations for AEs, will be displayed to the nearest integer.

Formatting for dates and times will follow the International Organization for Standardization (ISO) 8601 format:

- Dates only – yyyy-mm-dd
- Times only – hh:mm or hh:mm.ss
- Dates and times – yyyy-mm-ddThh:mm or yyyy-mm-ddThh:mm:ss

In general, for by-visit summaries, data recorded will be presented for the nominal visit. Unscheduled measurements will not be included in by-visit summaries, but will be eligible to contribute to the End of Study (EOS) value, will be included in the determination of best/worst case values (eg, shift tables) and will appear in listings.

Subjects who discontinue IP prematurely, having signed informed consent, will be followed for AEs as specified in the protocol and complete early termination procedures, which are the same as those conducted at Visit 7 (Day 29). Subjects who have discontinued IP early should continue to be followed for safety through Visit 8 (Day 60).

Listings will include scheduled, unscheduled, retest and early discontinuation data where recorded.

Any deviations from the analyses in this SAP will be identified in the CSR.

7.1 Multicenter Studies

The study is planned to be conducted at approximately 38 sites in the United States, Germany, Hungary, the Netherlands and Israel. Some exploratory subgroup analyses will be performed by country. Data from all participating sites will be pooled prior to analysis.

A summary of enrolment by site will be produced.

7.2 Treatment Descriptors

The treatment descriptors are “CSL112 6g” and “Placebo”.

7.3 Multiple Comparisons and Multiplicity

No statistical hypothesis testing will be performed in this study, therefore no adjustments for multiplicity will be made.

8 Data Handling Conventions

Treatment assignments will be applied to the clinical data at the time of the Database Lock based on the randomization schedule, which will be merged using the Randomization Number obtained from the eCRF to obtain the correct treatment assignment.

8.1 Missing Data

Missing data occurs when any requested data are not provided, leading to blank fields on the electronic case report form (eCRF). These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data.

8.1.1 Imputation of Non-Date Missing Data

Data from assessments that are not conducted because a subject withdrew from the study at any time or permanently discontinued study treatment, before completing all infusions, will not be considered missing data and no imputation for such values will be done.

Subjects with the designation of treatment relationship for AEs and SAEs missing will have the worst case assumed to impute the relationship; ie, if the investigator’s assessement of relationship to study treatment is missing it will be assumed to be “Yes”. There will be no other imputation for missing data other than as described in Section 8.1.2 for partial dates and times.

In the event that the study is terminated early, all available data will be listed and a review carried out by the study team to assess which statistical analyses are to be performed.

8.1.2 Imputation of Partial Dates

Imputed dates are used for slotting events to the appropriate study time periods and for sorting in data listings and will not be used to derive relative day, duration (eg, duration of AEs), or elapsed time variables and as a result will not displayed in any listings.

Partial date imputation will follow 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 AEs and medications are below.

Adverse Events

If an AE start or end date is either completely or partially missing, then the duration of the AE will be set to missing.

Date	Missing Element(s)	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 the study treatment start date.
	Day and Month.	• If the study treatment start date is not missing: → If the year of the AE start date is the same as the year of study treatment start date then ▪ If the AE end date indicates the AE ended prior to the study treatment start date then set the AE start date to January 1. ▪ Otherwise set the AE start date to the study treatment start date. • Otherwise set the AE start date to January 1.

Date	Missing Element(s)	Rule
	Day Only	• If the study treatment start date is not missing: → If the month and year of the AE start date are the same as the month and year of study treatment start date then ▪ If the AE end date indicates the AE ended prior to the study treatment start date then the AE start date to the 1st of the month. ▪ Otherwise set the AE start date to the study treatment start date. • Otherwise set the AE start date to the 1st of the month.
End Date	Day, Month, and Year	• No imputation for completely missing AE end dates; as applicable, report the AE as ongoing and the AE duration as missing.
	Any Partial Date	• No imputation for partial AE end dates; as applicable report the date as recorded and the AE duration as missing.

Concomitant Medications:

Imputations in the concomitant medication dataset will be performed for start and end dates as necessary to derive the prior/concomitant nature of the medication. Imputed dates will be recorded in the concomitant medication analysis dataset with a flag variable as previously described to indicate the level of imputation. The start and end dates will be used to classify medications as taken prior, during, and/or after study treatment.

Date	Missing Element	Rule
Start Date	Day, Month, and Year	• Do not impute completely missing medication start dates; all values that depend on this date will be set to missing. → The medication will be deemed to be a prior medication if the medication end date indicates that the medication could not have started after study treatment start. → Otherwise the medication will be deemed to be concomitant.
	Day and Month	• If the study treatment start date is not missing: → If the year of the medication start date is the same as the year of the study treatment start date then ▪ If the medication end date indicates the medication ended prior to the study treatment start date then set the medication start date to January 1. ▪ Otherwise set the medication start date to the study treatment start date. • Otherwise set the concomitant medication start date to January 1.

Date	Missing Element	Rule
	Day Only	• If the 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 the study treatment start date then ▪ If the medication end date indicates the medication ended prior to the study treatment start date then set the medication start date to the 1st of the month. ▪ Otherwise set the medication start date to the study treatment start date. • Otherwise set the medication start date to the 1st of the month.
End Date	Day, Month and Year	• Do not impute completely missing medication end dates; all values that depend on this date will be set to missing. → The medication will be deemed to be concomitant and ongoing.
	Day and Month	• If the medication partial end date contains the year only, set the medication end date to the earliest of [December 31, or the date of the last completed Safety assessment visit including subject completion, date of withdrawal from the study, date of loss to follow-up].
	Day Only	• If the partial medication end date contains the month and year, set the medication end date to the earliest of [the last day of the end month reported, the date of the last completed Safety assessment, date of withdrawal from the study or date of loss to follow-up].

If the start or end dates of a medication is recorded as "unknown" these will be treated as missing for the purposes of assigning as prior or concomitant.

8.2 Derived Variables

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

8.2.1 Reference Dates

The safety reference date is defined as the date of the first infusion of study treatment. This safety reference date will be used to assign study periods relative to study treatment.

8.2.2 Study Day and Relative Day for Safety Measures

Data presentations by visit, will use scheduled visits. For example, Visit 7 is targeted to occur at scheduled Study Day 29 but due to the visit window, may occur at Relative Day 31. It should be noted that Relative Day is distinct from Study Day, and that there is no Relative Day 0.

Relative Day will be calculated from the start of first infusion (time zero [0 h] on Study Day 1) as;

If the date of the assessment/event is on or after the date of start of first infusion then:

- Relative Day = (date of assessment/event – date of start of first infusion) + 1.

If the date of the assessment/event is prior to the date of start of first infusion then:

- Relative Day = (date of assessment/event – date of start of first infusion).

Relative Day will be used to show start/stop day of assessments and events, and will appear in every listing where an assessment date or event date appears.

In the situation where the assessment/event date is partial or missing, Relative Day, and any corresponding durations will appear missing in the listings.

8.2.3 Durations

Durations of events (eg, the duration of an AE or a medication) will be calculated in days using the following formula:

- (End Date – Start Date) + 1.

Durations calculated in days will use dates only.

Duration of infusions will be calculated in hours (h) using the following formula:

- (End Date/Time – Start Date/Time).

Other durations in the study will be presented (eg, ECG parameters); however, as these values come directly from raw data and no calculation is required, these are not detailed in this document.

8.2.4 Baseline Definition

Baseline for both laboratory and non-laboratory data is defined as the most recent pre-infusion, non-missing value prior to or on the date of first study treatment infusion.

8.2.5 Change from Baseline

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

Change from baseline for safety measures will be calculated as:

- Visit value – Baseline value.

Percentage change from baseline will be calculated as:

- ((Change from baseline) / Baseline value) * 100

If either the baseline or visit value are missing, then the change from baseline and percentage change from baseline will also be set to missing.

8.2.6 Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation).

Unscheduled serum creatinine assessments form a critical part of the co-primary endpoint for AKI identification. After an initial elevation (≥ 0.3 mg/dL) is observed, an unscheduled repeat measurement should occur no earlier than 24 hours after the initial elevation. See Section 11.1 for the details of the programming algorithm for identification and confirmation of events.

All 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.

8.2.7 Actual Treatment

The subjects' actual treatment will be assigned from the "End of Study (Unblinded Data File)" as a data extract from the IRT. The external vendor, Cenduit, will provide this file to Quintiles after confirmation of Database Lock. Reconciliation of kit numbers and materials dispensed/infused was conducted within the IRT. Further details on the contents of this file are provided in Section 10.3 of the User Requirements Specification (URS) v9.0 dated 8th March 2017.

In the event that a subject receives a study treatment that is different from the assigned treatment, then assigning the actual treatment received will follow this rule:

- CSL112 6g overrides Placebo

For example, if a subject had 3 doses of Placebo and a single dose of CSL112 6g, then the actual treatment assignment would be CSL112 6g.

8.2.8 Derived Variables

Derivation of Body Mass Index (BMI)

BMI will be calculated using the following formula:

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

Using the height measured at Screening and the weight measured at Day 1 (if available). If weight at Day 1 is not available, the assessment at Screening will be used (if available). If neither is available, then BMI is missing.

Derivation of Direct Bilirubin (Local)

The calculation of Direct Bilirubin is only applicable when both Total Bilirubin and Indirect Bilirubin are given in the raw local laboratory data. No calculation of Indirect Bilirubin is required.

$$\text{Direct Bilirubin (µmol/L)} = \text{Total Bilirubin (µmol/L)} - \text{Indirect Bilirubin (µmol/L)}$$

Derivation of eGFR

For the purpose of safety analysis, the eGFR value will be recalculated using the Visit 2 (Day 1, Before Infusion) serum creatinine values from the Central Laboratory for eGFR (Central) and the Local Laboratory for eGFR (Local) using the CKD-EPI equations in Table 1:

Table 1: CKD-EPI Equations

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

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

- $eGFR = 141 \times \min(SeCr/\kappa, 1)^{\alpha} \times \max(SeCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black],

where SeCr 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 SeCr/κ or 1, and max indicates the maximum of SeCr/κ or 1. In Table 1: the multiplication factors for race and sex are incorporated into the intercept, which results in the different intercepts for age and sex combinations.

Derived eGFR values will be presented to two decimal places.

8.2.9 Study Time Periods for Other Medications

Medications, other than study treatment, will be designated as "Prior" and/or "Concomitant" based on start and end dates relative to first dose of study treatment. For instances where the medication date is either partial or missing, refer to Section 8.1.2.

Designate as "Prior" if the medication start date is prior to study treatment start date; if subject has not taken any study treatment; or the medication start date is missing.

Designate as "Concomitant" if the medication start date is before the study treatment end date and the medication end date is either after the study treatment start date or missing.

Note that a medication may be both "Prior" and "Concomitant, ie, the categories are not mutually exclusive.

Baseline medications are defined as 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).

Prior to Index MI medications are defined as those medications that either ended or were ongoing 1 day prior to the date of the subjects Index MI event.

8.3 Values of Potential Clinical Importance

8.3.1 Laboratory Parameters

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

Increases in specific laboratory values associated with the secondary endpoints are:

- Absolute changes from baseline in serum creatinine:
  - → ≤ Baseline value
  - → > 0 to <0.3 mg/dL
  - → ≥ 0.3 to ≤ 0.5 mg/dL †
  - → > 0.5 mg/dL †

† Potential clinical significance.

- Increases in serum creatinine sustained for ≥ 24 hours upon repeat measurement:
  → ≥ 1.5x baseline value,
  → ≥ 2.0x baseline value.
  → ≥ 3.0x baseline value
  → ≥ 4.0 mg/dL (353.6 µmol/L)

  An additional summary will be presented for single instances of increases in serum creatinine, i.e. without assessment of whether those increases were sustained.

- A decrease in eGFR (Central) ≥ 25% from baseline starting during the Active Treatment Period and that is sustained at the final study visit

- Changes from baseline in hepatic status that occur during the Active Treatment Period and that are sustained for ≥ 24 hours upon repeat measurement as follows:
  → ALT > 3x ULN,
  → ALT > 5x ULN,
  → ALT > 10x ULN
  → Serum Total Bilirubin † > 1.5x ULN,
  → Serum Total Bilirubin † > 2x ULN

  An additional summary will be presented for single instances of increases, i.e. without assessment of whether those increases were sustained.

† Note that for subjects with a history of Gilbert's syndrome, serum bilirubin assessments will be based on direct bilirubin. The calculation of direct bilirubin for local laboratory values is given in Section 8.2.8.

Secondary endpoints as specified in the protocol section 2.2 include clinically significant changes in clinical laboratory test results (serum biochemistry, hematology, and urinalysis) with Grade 3 and 4 Laboratory Abnormalities, as potentially clinically significant laboratory test results, see Table 9:.

8.3.2 ECG Parameters

Abnormal quantitative ECG measurements will be identified in accordance with the predefined markedly abnormal criteria in Table 2:.

Table 2: Markedly Abnormal Quantitative ECG Measurements

ECG parameter	Markedly Abnormal Change
QT uncorrected, QTcB and QTcF	>450 msec
	>480 msec
	>500 msec
	>30 msec increase from baseline
	>60 msec increase from baseline
Heart rate	≥ 120 bpm during active treatment and an increase of ≥15 bpm from baseline
	≤ 50 bpm during treatment and a decrease of ≥15 bpm from baseline
PR/QR interval	<120 msec during treatment and a normal baseline value
	>210 msec during treatment and a normal baseline value
QRS	>110 msec during treatment and a normal baseline value

8.3.3 Vital Signs

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the predefined markedly abnormal criteria detailed in Table 3: in Section 8.3.3.

Table 3: 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
Body Temperature	˚C	NA	≥ 38.3 ˚C AND an increase from baseline ≥ 1.1
Weight	kg	Percentage decrease from baseline ≥ 7.0 %	Percentage increase from baseline ≥ 7.0 %

9 Study Population

9.1 Disposition of Subjects

Summary tables with columns identified by IP group: (CSL112 6g, Placebo, Total) will be produced for the following;

- Total number of subjects in each of the analysis populations described in Section 6.
- Total number of subjects in each of the 4 randomization strata: eGFR 30 - <45 mL/min/1.73 m^2 or 45 - <60 mL/min/1.73 m^2 and by medical history of diabetes requiring current treatment with any anti-diabetic medication (yes or no).
- Study treatment status, including subjects who completed the study (defined as all subjects who completed Visit 8 (Day 60)), discontinued IP (including reasons for discontinuation), or withdrew consent for the study.
- Subject completion by visit.
- Subjects screened, (including screen failures) and subjects randomized to IP.
- Duration of Follow-up, ie, the time from randomization to last contact.

Reasons for study withdrawal and study treatment discontinuation will be presented in the order they are displayed in the eCRF.

The following details will be provided in listings:

- Screen failure subjects, including reason for screening failure.
- Reasons for study withdrawal including the date of withdrawal.
- Reasons for study treatment discontinuation. The listing will include last dose date, cumulative dose, and reasons for study treatment discontinuation.
- Reasons for discontinuation of IP and withdrawal of consent from the study will be listed for each such subject.
- Differences between actual treatment received and randomized, as well as between strata allocation based on central laboratory values (derived) and the randomized assignment.

9.2 Protocol Deviations

All instances of deviations from the protocol will be documented in the Clinical Trial Management System (CTMS) log. A deviation occurs when an investigator site, or study subject, does not adhere to protocol stipulated requirements. Deviations will be assessed by CSL as they are reported and categorized as either Major or Minor.

Both Major and Minor protocol deviations for subjects in the ITT population will be summarized, displaying the number and percentage of subjects with any protocol deviation as well as the categories for the deviations. All protocol deviations will be listed.

Refer to the Protocol Deviation Management Plan (v1.0 dated November 1st 2016) for complete details on the handling of protocol deviations.

A further by subject listing will be prepared for deviations related to infusion durations. The following deviations will be identified programmatically:

- Infusion duration < 2 hours and the infusion rate exceeds 3 mg/kg/min of sucrose.
- Infusion duration > 3 hours and
  - → < 80% volume of IP was administered, or
  - → > 120% volume of IP was administered.

CCI

CCI

CCI

Additional by subject listings will be produced for subjects who:

- Received IP different to their randomized treatment
- Were randomized but did not meet eligibility criteria
- Were allocated to the incorrect stratum in IRT based on the eGFR (Local) value.
- Were allocated to the incorrect stratum in IRT based on the Medical History data for Diabetes Mellitus.

The eGFR (Local) value will be calculated using the local laboratory baseline serum creatinine, age, sex, and race. For the derivation of eGFR see Section 8.2.8.

- eGFR (Local)
  - → < 30 mL/min/1.73 m^2
  - → 30 - < 45 mL/min/1.73 m^2
  - → 45 - <60 mL/min/1.73 m^2
  - → ≥ 60 mL/min/1.73 m^2

9.3 Eligibility Criteria

A summary of Inclusion/Exclusion criterion failed for screen failures in addition to a by subject listing will be produced. As subjects may fail to meet more than one Inclusion and/or Exclusion criterion, the percentages across criteria may not sum to 100%.

9.4 Demographic and Baseline Characteristics

The following demographic data will be summarized by treatment group:

- Age (years)
  - → 18 to < 65,
  - → ≥ 65 to < 75,
  - → ≥ 75 to < 85,
  - → ≥ 85

In addition to summarization as a categorical variable, age (years) will also be summarized as a continuous variable.

- Sex
- Ethnicity
- Race

For subjects reporting more than one Race category, classify as "Racial Combination" group.

- Country

The following baseline characteristics will be summarized by treatment group for the ITT population.

- Height (cm)
- Weight (kg)
- BMI (kg/m^2) (See Section 8.2.8)
- eGFR from IRT using Local Laboratory data from Visit 2 (or Screening).
  - → 30 - < 45 mL/min/1.73 m^2
  - → 45 - < 60 mL/min/1.73 m^2

The eGFR (IRT) value will be calculated by the IRT from the serum creatinine obtained by the local laboratory at Visit 2, or Screening if the screening visit and randomization occur on the same day.

- eGFR (Central)
  - → < 30 mL/min/1.73 m^2
  - → 30 - < 45 mL/min/1.73 m^2
  - → 45 - <60 mL/min/1.73 m^2
  - → ≥ 60 mL/min/1.73 m^2

The eGFR (Central) value will be calculated using the central laboratory baseline serum creatinine, age, sex, and race. For the derivation of eGFR see Section 8.2.8.

The eGFR (Central) values will be summarized both categorically using these groupings and as a continuous variable using univariate statistics. A summary of the agreement between randomized and derived strata allocation will be produced.

- Disease characteristics at screening.
  - → Type of Index MI
    - ST Segment Elevation Myocardial Infarction (STEMI)
    - Non-ST Segment Elevation Myocardial Infarction (NSTEMI)

The following targeted medical history will be summarized by treatment group for the ITT population.

- Prior MI
- Stable angina
- Unstable angina
- Coronary revascularization or surgery (prior to Index MI)
- Congestive heart failure
- Peripheral artery disease
- Clinically significant valvular heart disease
- Clinically significant heart rhythm disorder
- Cerebrovascular disease
- Clinically significant bleeds
- Hypertension
- Gilbert's Syndrome
- Chronic kidney disease
- Dyslipidemia or use of treatment for dyslipidemia
- Diabetes mellitus
- Smoking/tobacco use

All other medical history within 3 months before the screening visit is entered into the eCRF as free text and will be coded using MedDRA version 20.0 and summarized by treatment group, System Organ Classes (SOC) and PT. By subject listings for all medical history data will also be produced.

- Baseline Medications of Interest
  - → Aspirin
  - → Anti-thrombotics
  - → Anti-platelets
  - → Beta blockers,
  - → Angiotensin-Converting-Enzyme Inhibitor (ACE-I) or Angiotensin Receptor Blockers (ARB).
  - → Anti-hyperlipidemic
    Consisting of statins and other lipid modifying agents.

For the timing rules regarding identification of medications being taken at baseline, refer to Section 8.2.9. An external source dataset (Excel format) containing the full set of individual medications of interest will be provided by CSL.

- Baseline Statin Use
  - → High dose/intensity
  - → Moderate dose/intensity
  - → Low dose/intensity
  - → None

Table 5: contains the anatomical therapeutic chemical (ATC) and World Health Organization drug dictionary (WHODD) codes in addition to the dose thresholds for identifying the moderate and high dose/intensity statins (Stone NJ, et al, 2014).

Table 5: Identification of Moderate and High Dose/Intensity Statins

Preferred Name	WHODD Code	ATC Level 4 Code	ATC Level 4 Text	Daily Dose Threshold	
				Moderate Intensity	High Intensity
ATORVASTATIN	1326101001	C10AA	HMG COA REDUCTASE INHIBITORS	≥10 to <40 mg	≥ 40mg
LIPITOR	1326102016				
ATORVASTATIN CALCIUM	1326102001				
ROSUVASTATIN	1588601001	C10AA	HMG COA REDUCTASE INHIBITORS	≥5 to <20 mg	≥ 20mg
CRESTOR	1588602002				
ROSUVASTATIN CALCIUM	1588602001				
SIMVASTATIN	848101001	C10AA	HMG COA REDUCTASE INHIBITORS	≥20 to <80 mg	≥ 80mg
ZOCOR	00848101004	C10AA	HMG COA REDUCTASE INHIBITORS		≥ 80mg
PRAVASTATIN	880401001	C10AA	HMG COA REDUCTASE INHIBITORS	≥ 40mg	
LOVASTATIN	896701001				
FLUVASTATIN	1224501001	C10AA	HMG COA REDUCTASE INHIBITORS	≥ 80 mg	
FLUVASTATIN XL	1224502107				
PITAVASTATIN	6470001001	C10AA	HMG COA REDUCTASE INHIBITORS	≥ 2 mg	
INEGY (ezetimibe and simvastatin)	1726001001	C10BA	HMG COA REDUCTASE INHIBITORS IN COMBINATION WITH OTHER LIPID MODIFYING AGENTS		≥ 10mg and ≥ 40mg, respectively
VYTORIN (ezetimibe and simvastatin)	1726001002				
EZETIMIBE W/SIMVASTATIN	1726001003				
EZETIMIBE /SIMVASTATIN	1726001029				

Subjects with simultaneous use of the medications in Table 6: will be considered to be on a high dose/intensity statin. Use of either drug at these levels without the other does not constitute high dose/intensity statin use.

Table 6: Identification of Combination High Dose/Intensity Statins

Preferred Name	WHODD Code	Daily Dose Threshold
		High Intensity
EZETIMIBE and SIMVASTATIN	01587001001 00848101001	≥ 10mg and ≥ 40mg, respectively
EZETIMIBE and ZOCOR	01587001001 00848101004	
ZETIA and SIMVASTATIN	01587001003 00848101001	
ZETIA and ZOCOR	01587001003 00848101004	
EZETROL and SIMVASTATIN	01587001002 00848101001	
EZETROL and ZOCOR	01587001002 00848101004	

Summary statistics on the following timing durations, overall and by country will also be presented:

- Index MI to Angiography
- Angiography to Randomization
- Angiography to First Infusion
- Randomization to First Infusion
- Index MI to First Infusion
- Angiography to Local Laboratory Sample used to Determine Eligibility

The following listings will be provided:

- Demographic characteristics
- Race
- Pregnancy testing
- Follicle Simulating Hormone (FSH) testing
- Targeted and non-targeted medical history
- Medications of Interest

- Medications of Interest taken the day prior to Index MI,
- Medications of Interest taken after Index MI and continuing at Randomization.
- Use of renal replacement therapy

Renal replacement therapy will be identified using the MedDRA terms in Table 7: and must begin after the start of the first infusion and no later than the end of the Active Treatment Period.

Table 7: Qualifying Renal Replacement Therapies

MedDRA Preferred Term Code	MedDRA Preferred Term
10061105	Dialysis
10034660	Peritoneal dialysis
10018875	Haemodialysis
10066338	Continuous haemodiafiltration
10038533	Renal transplant

9.5 Concomitant Medications and Procedures

Medications will be coded using the WHODD (1st March 2017 Enhanced Version). They will be summarized in alphabetical order of generic term and grouped by the ATC code. Procedures will be coded using MedDRA version 20.0 and will be summarized in alphabetical order of PT. The summaries of medications and procedures will show the number and percentage of subjects taking the medications/receiving the procedures.
Listings based on the ITT population will also be provided.

Medications other than study treatment, and procedures will be designated as “Prior” and/or “Concomitant” based on the start and end dates relative to first dose of study treatment as described in Section 8.2.9.

Note that a medication may be designated as both “Prior” and “Concomitant, ie the categories are not mutually exclusive.

Prohibited medication use will be monitored by the CSL medical monitoring team via regular review of the medication data. If any prohibited medications are discovered they will be entered into the CTMS protocol deviation log, under the deviation category of “Concomitant Medication Criteria”.

Individual summaries of both prior and concomitant medications and procedures will be produced. Subjects with multiple instances of the same medication/procedure will be counted only once in each designation of prior or concomitant.

10 Efficacy

No efficacy analyses will be performed.

11 Safety Analyses

All safety analyses will be based on the SAF as defined in Section 6.

11.1 Co-primary Endpoints

The renal safety profile of CSL112 in subjects with moderate RI and AMI who receive up to 4 weekly administrations of CSL112 6g will be assessed by co-primary endpoints of the incidences of:

- Treatment-emergent renal SAEs,
- Treatment-emergent AKI

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

Note that treatment emergent renal SAEs can occur at any time on or after the first infusion, whilst AKI events must occur within the Active Treatment Period.

Renal Serious Adverse Events

Treatment-emergent is defined as occurring anytime on or after the start of the first infusion through to the end of the study.

A renal SAE is defined as any SAE with a MedDRA PT included in the following;

- Acute Renal Failure narrow SMQ (See Section 13.6.1)
- Renal Tubular Necrosis
- Renal Cortical Necrosis
- Renal Necrosis
- Renal Papillary Necrosis

Any renal SAE reported between the start of the first infusion and a subject's final study visit will be a co-primary endpoint event.

Non-serious AEs with any of the above MedDRA PTs do not form part of the Co-Primary Endpoint.

Acute Kidney Injury

Baseline for determination of AKI is defined as the pre-infusion central laboratory serum creatinine level on Study Day 1.

AKI is defined as an absolute increase in serum creatinine from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period (See Section 4.1.2.) that is sustained upon repeat measurement by the central laboratory no earlier than 24 hours after the elevated value. If no repeat value is obtained during the Active Treatment Period (eg, due to loss to follow-up or a protocol violation), a single serum creatinine value that is increased from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment Period would also fulfil the definition of AKI.

To identify a subject with an AKI event the following logic will be applied. Note that any given subject may have more than one AKI event during the Active Treatment Period:

1. Calculate the change from baseline (mg/dL) for each post-baseline serum creatinine value (including unscheduled assessments) during the Active Treatment Period.

2. Order the change values from the earliest to the latest by date and time.

3. Evaluating from the earliest to the latest visit, identify the initial increase from baseline of ≥ 0.3 mg/dL.

    a. If the following change from baseline value is also ≥ 0.3 mg/dL, and is at least 24 hours after the date and time of the initial increase, then the subject is confirmed to have an AKI event.

    b. If the following change from baseline value is < 0.3 mg/dL and is at least 24 hours after the initial increase, then this is not an AKI event.

    c. If the following change from baseline value is < 24 hours after the initial increase, this value should be discounted and the next value in the ordered sequence assessed.

d. If no repeat value at least 24 hours after the initial increase (within the Active Treatment Period) is obtained, then this single increase would also fulfil the definition of AKI.

The end date of the identified AKI event will be determined using the following algorithm for each subject with at least one AKI event:

1. Evaluating from the first confirmed increase, determine if there are 2 consecutive change from baseline values < 0.15 mg/dL (ie, with no interspersed changes ≥ 0.15 mg/dL), each at least 24 hours from the preceding change from baseline value.

2. If there are 2 consecutive change from baseline values that are < 0.15 mg/dL at least 24 hours apart, then the end date of the AKI event is the date and time of the first increase of these 2 consecutive change from baseline values < 0.15 mg/dL.

3. If the subject does not have 2 consecutive change from baseline values that are < 0.15 mg/dL after a confirmed increase, then the end date of the AKI event is missing.

After identifiying the first AKI event for a subject and assessing its end date, the algorithms will then be applied to the remaining serum creatinine change values following the initial AKI event to identify any further instances of AKI events for a given subject.

If a subsequent AKI event occurs, and is within 48 hours of the previous event ending, then this will be designated as one single event. This will be determined as follows;

1. If the start date and time of the subsequent AKI event is at least 48 hours after the end date and time of the previous AKI event, then the subject is confirmed to have a further instance of an AKI event.

2. If the start date and time of the subsequent AKI event is within 48 hours of the end date and time of the previous AKI event, then this is deemed to be the same event.

    a. The end date and time of the original AKI event will then be replaced with the end date and time of the subsequent AKI event, provided there are no further AKI events within 48 hours of its end date and time. No changes are required to the start date and time of the original AKI event.

11.2 Analysis of Co-primary Endpoints

Analysis of the co-primary endpoints will take place at study completion (when all randomized subjects either complete Visit 8/Study Day 60, have withdrawn from the study, or have been lost to follow-up) or after the study is terminated early based on recommendation of the independent DSMB and endorsement by the Steering Committee).

For each co-primary endpoint, a Newcombe-Wilson two-sided 95% confidence interval around the difference in incidence rates will be calculated if at least one event occurs. Otherwise, an exact, one-sided, upper 97.5% confidence interval will be reported for the incidence rate in each treatment arm.

The following will be produced:

- Summaries of the co-primary analysis results. The point estimates of the differences in incidence rates between treatment arms will be provided for each co-primary endpoint separately, along with the Newcombe-Wilson two-sided 95% confidence intervals when at least one event occurs, or otherwise if no event occurs, with the exact, one-sided, upper 97.5% confidence intervals for the incidence rates in each of the treatment arms.

- A summary including the number of AKI events per subject and subject counts for the following day intervals for the duration of AKI events.

  → 1-7
  → 8-14
  → 15-21
  → 22-28

- A summary of co-primary Renal SAE PTs including the breakdown of information as adjudicated by the CEC.

- A listing of creatinine values for subjects with any AKI events.

- A listing of all AKI events including subject ID, treatment group, change from baseline (mg/dL) in serum creatinine, start date, end date, and duration.

- A listing of all AEs for subjects with any renal SAE.

- Box plots by visit, showing actual and change from baseline values in serum creatinine, as well as eGFR (Central).

- Individual subject series plots of the change from baseline in both central and local laboratory serum creatinine over time, for subjects with at least one central laboratory change from baseline ≥ 0.3mg/dL.

11.2.1 Sensitivity Analyses of Co-primary endpoints

A sensitivity analysis of the co-primary endpoints will use independently adjudicated results for the treatment-emergent renal SAE component and local laboratory data for the treatment-emergent AKI component. The same methods as for the primary study analysis described in Section 11.2 will be used.

A further two sensitivity analyses will be performed, the first will include all absolute increases in serum creatinine from baseline ≥ 0.3 mg/dL (26.5 µmol/L) during the Active Treatment regardless of confirmation. That is the initial increase of 0.3 mg/dL will be enough to qualify as an event for analysis. The same methods as for the primary study analysis described in Section 11.2 will be used.

The second of these sensitivity analyses will repeat the primary analyses, whilst excluding increases in serum creatinine from baseline ≥ 0.3 mg/dL (26.5 µmol/L) that had a missing confirmatory assessment. That is any increase that was identified as a primary endpoint due to no repeat value being obtained, will be excluded from this sensitivity analysis.

In a separate sensitivity analysis, AKI rates will be compared among subjects whose dosing eligibility was determined in part based on serum creatinine determinations performed 12 to 24 hours after radiographic contrast exposure versus those performed 48± 6 hours after radiographic contrast exposure.

In the event that there are insufficient observations to perform this analysis, (defined as fewer than 15 subjects observed within each timing group) then comparison of the AKI rates among subjects whose dosing eligibility was determined in part based on serum creatinine determinations performed 12 to 48 hours after radiographic contrast exposure versus those performed > 48 hours will be explored.

For either analysis, the difference in placebo-corrected rates between the 2 time-period subgroups will be calculated, along with a 2-sided adjusted Wald 95% confidence interval (Price, Bonett, 2004).

Timing of Serum Creatinine Determinations Algorithm

The following is the algorithm for calculating the time between contrast and the local laboratory sample used for determining eligibility, which will be used in the sensitivity analysis:

- Timing (hours) = Scr Date/Time – (Con Date/Time) where;

  → Scr is the Sample Collection Date/Time, as reported on the LOCAL1 (or LOCAL4 if Visit 1 and Visit 2 were combined) page of the eCRF, for the Serum Creatinine Value, and

  → Con is the Date and Time Contrast was Given, as reported on the INDEXMI page of the eCRF.

11.2.2 Subgroup Analyses of Co-primary Endpoints

Summaries of co-primary endpoint events and of renal SAEs and AKI events separately will be produced by treatment group for:

- Subjects with eGFR (Central) of <30 mL/min/1.73 m^2
- Subjects with eGFR (Central) of 30 - <45 mL/min/1.73 m^2
- Subjects with eGFR (Central) of 45 - <60 mL/min/1.73 m^2
- Subjects with eGFR (Central) of >60 mL/min/1.73 m^2
- Subjects with medical history of diabetes requiring current treatment with any anti-diabetic medication
- Subjects without medical history of diabetes requiring current treatment with any anti-diabetic medication.

The differences in incidence rates between treatment arms will not be provided for the subgroup summaries.

11.3 Extent of Exposure

Exposure to IP will be presented for the SAF by treatment group, by infusion and overall. The following will be summarized as well as listed, by treatment group:

- Number of infusions administered per subject
- Number of infusions completed per subject
- Locale for IP Administration

In addition to the above, the following items will be summarized for the by infusion summaries;

- Duration of infusions (minutes)
- Number of days between infusions
- Actual volume infused (mL)
- Number of interruptions per infusion

By-subject listings will include, in addition to tabulated data, details regarding infusion modifications, interruptions and any overdoses.

11.4 Adverse Events

Adverse Events will be coded using the MedDRA central coding dictionary, Version 20.0 and graded in accordance to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. If an event has a missing CTCAE grade, the AE will be assumed to have a grade of 3 for reporting purposes.

All summaries of AEs will include all treatment-emergent AEs (TEAEs), defined as AEs reported at or after the start of the first infusion and presented by SOC and PT. Subjects who have more than one AE recorded for the same PT will only be counted once within that PT. Subjects with multiple PTs will contribute to each PT summary but only once in the overall SOC row.

Summaries of TEAEs will count the number of subjects, not the number of events, that is, subjects with multiple occurrences of the same TEAE will be counted only once.

An overview summary of TEAEs will be produced, including counts and percentages of subjects as well as the number of events, with any:

- TEAE
- Study treatment related TEAE
- Study procedure related TEAE
- Serious TEAE
- Study treatment related serious TEAE
- Fatal TEAE
- Study treatment related fatal TEAE
- TEAE with CTCAE Grade ≥ 3
- Line items for TEAEs of special interest identified by PTs (See Section 11.5)
  → Bleeding Events

→ Potential Hemolysis as Identified Using the Haemolytic Disorders SMQ
→ Drug Hypersensitivity Reactions

- Suspected adverse drug reaction (See Section 11.8)
- TEAE leading to study withdrawal
- TEAE leading to permanent discontinuation of study treatment;
- TEAE leading to dose delays
- TEAE leading to dose interruptions
- TEAE leading to skipped doses

The frequency and percentage of TEAEs for each line item of the overview summary will be summarized in descending order of incidence in the CSL112 6g treatment group by PT only. Selected line items will be summarized by SOC and PT.

Missing relationship to study treatment will be imputed as described in Section 8.1.1.

The following summaries will be provided in support of the information described above for TEAEs:

- TEAEs by PT and Maximum Grade
- TEAEs by PT for subgroups based on eGFR (Central) value at the time of randomization.
- TEAEs by PT for subgroups based on diabetic status at the time of randomization

All AEs, regardless of when they were reported, will be listed. Listings will include Subject ID, Derived Stratification Group SOC, Preferred and Verbatim Terms, Relative Start, End and Duration, Severity Grade, SAE (yes or no), Relationship to Treatment, Relationship to Procedure, Any Action Taken and the Outcome of the AE.

The following listings will be provided:

- AEs
- AEs of CTCAE Grade 3 or Higher
- AEs by Treatment showing Subjects Experiencing each PT
- AEs Among Subjects who were Screened but not Treated

11.5 Adverse Events of Special Interest (AESI)

The following types of AEs are of special interest for which monitoring and/or expedited reporting by the Investigator is required:

- Stage 3 AKI
- Drug hypersensitivity
- Potential Hy's Law cases
- Hemolysis
- Bleeding events

To identify AESI of drug hypersensitivity, hemolysis and bleeding events in the database, a comprehensive list of MedDRA terms based on SMQs will be used to identify the PTs of interest. These are provided in Section 13.6.1.

Summaries by PTs for each of the AESI will be provided separately and consist of;

- AESI Overview for Drug Hypersensitivity Reaction
- Drug Hypersensitivity Reactions by PT
- AESI Overview for Hemolysis
- Hemolysis by PT
- AESI Overview for Bleeding Events as Reported by Investigators
- AESI Overview for Bleeding Events as Adjudicated by the CEC
- Bleeding Events as Reported by Investigators by PT

The following by subject listings will be provided:

- AESI - Drug Hypersensitivity Reactions
- AESI - Hemolysis
- AESI - Bleeding Events

11.5.1 Stage 3 Acute Kidney Injury

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

No identification of Stage 3 AKI will be performed using PTs reported by the investigator, see Section 11.10.3 for further details.

11.5.2 Drug Hypersensitivity

If a drug hypersensitivity reaction is suspected, it should be reported as an AE by the investigator. The list of PTs for identifying these drug hypersensitivity reactions are given in Section 13.6.2.

11.5.3 Potential Hy's Law Cases

Potential Hy's Law cases for the purpose of AESI identification will be defined as any elevation in ALT > 3x ULN with a concomitant increase in total bilirubin that is > 2x ULN that is confirmed by repeat assessment using the central laboratory data. Aspartate aminotransferase (AST) is not being used in this definition since there may be increases in AST that are due to the index MI event.

No identification of potential Hy's Law will be performed using PTs reported by the investigator, see Section 11.10.4 for further details.

11.5.4 Hemolysis

Potential hemolysis will be defined as a decrease in hemoglobin during the Active Treatment Period ≥ 2 g/dL from baseline using central laboratory data. See Section 11.10.5 for further details.

In addition, in order to rule out decreases in hemoglobin due to overt blood loss, the Haemolytic disorders SMQ (given in Section 0) will be used to identify hemolysis.

There will be separate summaries for events identified by these two methods.

11.5.5 Bleeding Events

Bleeding events will be assessed according to the BARC definition for bleeding events and will be independently adjudicated.

The list of PTs for identifying bleeding events of interest are given in Section 13.6.3.

11.6 Deaths and Serious Adverse Events

Adverse events leading to death are recorded on the AE page of the eCRF with an outcome of 'Fatal'. A tabular summary will be prepared displaying the number and percentage of subjects with a fatal AE and primary cause of death (disease under study, SAE related to study treatment, or other).

If there are no deaths on study, then this display will be produced with the text "*No deaths reported*". Deaths, if any, will also be listed. A supportive listing will be generated to provide subject-specific details on subjects who died.

If there are any deaths, the following summaries will be provided based on the number and percentage of subjects experiencing each unique PT:

- Fatal TEAEs by PT
- Fatal Study Treatment-Related TEAEs by PT

SAEs will be summarized based on the number and percentage of subjects experiencing each unique PT. The following summaries will be provided:

- Treatment-emergent SAEs by PT
- Study treatment-related treatment-emergent SAEs PT

The following listings to support the summaries described above will be provided:

- SAEs
- Fatal AEs
- Deaths Among Subjects who were Screened but not Treated

11.7 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 based on the number and percentage of subjects experiencing each unique PT:

- TEAEs Leading to Withdrawal from the Study, by PT
- TEAEs Leading to Permanent Discontinuation of Study Treatment, by PT
- TEAEs Leading to Infusion Delays, by PT
- TEAEs Leading to Infusion Interruptions, by PT
- TEAEs Leading to Skipped Infusions, by PT

The following listings to support the summaries described above will be provided:

- AEs Leading to Withdrawal from the Study
- AEs Leading to Permanent Discontinuation of Study Treatment
- AEs Leading to Infusion Delays
- AEs Leading to Infusion Interruptions
- AEs Leading to Skipped Infusions

11.8 Adverse Drug Reactions

An adverse drug reaction (or suspected adverse drug reaction) is defined as either:

a. A TEAE, including local tolerability events, that begin during or within 1 hour of the end of an infusion, or
b. A TEAE reported as causally related to the administration of study treatment, or which the sponsor determined to be causally related to the administration of study treatment, or
c. A TEAE for which the investigator's causality assessment is missing or indeterminate, or
d. All TEAEs for which the incidence in an active treatment arm exceeds the exposure-adjusted incidence rate in the placebo arm by 30% or more, provided the difference in incidence rates is 1% or more.

A summary of all suspected adverse drug reactions by SOC and PT will be provided along with a supportive by subject listing.

Exposure Adjusted Algorithm

For each PT recorded on the AE page of the CRF, the following algorithm will be applied to define whether or not the PT in question is an adverse drug reaction according to criterion d.

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

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

Therefore the PT will be considered an adverse drug reaction according to criterion d if and only if both of the following are true;

- Active IR-Placebo IR $\geq 1\%$.
- $\left(\frac{Active\ EAIR - Placebo\ EAIR}{Placebo\ EAIR} \times 100\right) \geq 30\%$, 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 (Active IR-Placebo IR) $\geq 1\%$.

For adverse drug reactions identified according to criterion d, all subjects experiencing that particular PT will be included in the summary and listing.

11.9 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 any subject or 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.

11.10 Clinical Laboratory Evaluations

Summaries for worst observations will include data from scheduled and unscheduled visits obtained from the central laboratory data. Other tabular summaries will only include data from scheduled visits obtained from central laboratory data, whilst listings will be prepared for both Central and Local laboratory data along with laboratory specific normal ranges.

For all summaries of clinical laboratory evaluations that reference a baseline value, the definition for the baseline assessment is in Section 8.2.4.

The denominator in any percentage calculations at each scheduled visit will be based on the number of subjects with a non-missing value at the respective visit.

Separate summary tables for hematology, chemistry, liver function, and urinalysis will be produced.

11.10.1 Hematology, Serum Biochemistry, and Liver Function from the Central Laboratory

The following parameters from the central laboratory will be summarized with descriptive statistics, by treatment group, and scheduled visit. All presentations will use International System (SI) Units.

Hematology	Serum Biochemistry	Liver Function

• Hemoglobin • Hematocrit • RBC Count and Indices • WBC Count, Total and Differentials → Basophils, → Eosinophils, → Lymphocytes, → Monocytes, → Neutrophils • Platelet Count	• Albumin • Total Protein • Creatinine • eGFR (Central) • Blood Urea Nitrogen (BUN) • Urate • Glucose • Calcium • Chloride • Sodium • Potassium • Bicarbonate	• Alkaline phosphatase • ALT • AST • Total Bilirubin • Direct Bilirubin • Indirect Bilirubin

Creatinine is collected using mg/dL, conversion to SI unit of µmol/L is required by multiplying using a factor of 88.4.

Glucose is collected using mg/dL, conversion to SI unit of mmol/L is required by multiplying using a factor of 18.018.

Quantitative laboratory measurements reported as "< X", ie, below the lower limit of normal (BLN), or "> X", ie, above the ULN, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, ie, as "< X" or "> X" in the listings.

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

The following summaries will be provided for laboratory data by treatment group:

- Actual and change from baseline by visit (for quantitative measurements)
- Shifts from baseline to worst observation in the Active Treatment Period according to normal range criteria (for quantitative measurements and

categorical measurements). The definition of "worst" is detailed in Table 8: for each parameter.

If a subject has a decrease to below the normal range and an increase to above the normal range during the same time interval, then the subject is counted in both the decrease to below the normal range and increase to above the normal range categories.

Table 8: Definition of Worst Observation by Parameter

Low	Low or High	High
Hemoglobin	Glucose	Alkaline Phosphatase ALT AST Total Bilirubin Direct Bilirubin Urine Protein

By-subject listings of subjects with results outside of the normal range in the Active Treatment Period will also be produced.

For the hepatic and renal laboratory parameters, namely ALT, total bilirubin, serum creatinine, and eGFR (Central) values for the change from baseline at each visit and by treatment group will be presented visually using box plots.

Grade 3 and 4 laboratory abnormalities defined in Table 9: will be designated as clinically significant. These will be summarized by time point and listed.

Table 9: Grade 3 and 4 Laboratory Abnormalities

Laboratory Parameter	Grade 3	Grade 4
Alkaline phosphatase	> 5 - 20x ULN	> 20x ULN
ALT	> 5 - 20x ULN	> 20x ULN

Laboratory Parameter	Grade 3	Grade 4
AST	> 5 -20x ULN	> 20x ULN
Total bilirubin	> 3x - 10x ULN	> 10x ULN
Direct bilirubin	> 3x - 10x ULN	> 10x ULN
Creatinine	> 3x Baseline > 3 - 6x ULN	> 6x ULN
Glucose	> 250 - 500 mg/dL	> 500 mg/dL
Hemoglobin	< 8 g/dL	N/A
eGFR	15 - < 30 mL/min/1.73m^2	< 15 mL/min/1.73m^2

The proportion of subjects who have missing serum creatinine results will be presented by visit and treatment group and for all subjects.

Individual subject series plots will be provided for all subjects who experience at least one instance of a central laboratory serum creatinine change from baseline ≥ 0.3mg/dL.

11.10.2 Hepatic Injury Assessment

If any subject has elevation in ALT > 3x ULN with a concomitant elevation in total bilirubin > 2x ULN OR an elevation in ALT > 5x ULN, blood samples should be obtained and sent to the central laboratory within 48 to 72 hours for further testing.

These parameters will be identified in the Central Laboratory data panel using the visit label (VISIT) of "Hepatic Injury Assessment". These unscheduled results will be included in the identification of "worst case" values and a listing of all results will be provided.

11.10.3 Stage 3 Acute Kidney Injury

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

11.10.4 Hy's Law

Hy's Law as defined in the Guidance for Industry: Drug-induced Liver Injury: Premarketing Clinical Evaluation (2009) is an elevation in AST or ALT > 3x ULN

with a concomitant increase in total bilirubin that is > 2x ULN without initial findings of cholestasis (elevated alkaline phosphatase, defined as > 2x ULN), and with no other reason found to explain the combination of these increased AST/ALT and total bilirubin findings.

Note that the AESI of Potential Hy's Law cases uses a definition that excludes AST values. For further details see Section 11.5.3.

A summary table for the concomitant elevations identified using the Central Laboratory data will be produced. Supportive by subject listings will display the Liver Function parameters from both Central and Local Laboratory data panels for subjects contributing to the summary table.

11.10.5 Hemolysis

If a post-infusion hemoglobin value is ≥ 2 g/dL below the baseline value and is not explained by overt blood loss, assessment for hemolysis should be performed by the central laboratory. The following parameters will be collected for suspected hemolysis, these data will be listed only. These unscheduled assessments will be included in the identification of any worst case values.

- Hemoglobin Level (Repeated)
- Total, Direct Bilirubin and Indirect Bilirubin (Calculated)
- Serum Haptoglobin
- Lactate Dehydrogenase (LDH)
- Urine Hemosiderin

11.10.6 Drug Hypersensitivity

If a drug hypersensitivity reaction is suspected, blood samples should be obtained and sent to the central laboratory for calculation of:

- Quantitative immunoglobulins (IgG, IgA, IgM, IgE)
  → If IgA is low or not detectable, then anti-IgA antibodies will be assayed
- Complete blood count with differential

These data will be listed only.

11.10.7 Local Laboratory Assessments

The local laboratory is to be used for all laboratory tests that must be reviewed in real time such as for study eligibility and dosing decisions. All laboratory test samples also go to the central laboratory for analysis.

Local laboratory data will be presented in the same format as for central laboratory results as well as being listed.

11.10.8 Urinalysis

To summarize the categorical results at baseline versus the maximum value observed during the Active Treatment Period, shift tables will be produced for the following parameters reported in the central laboratory data:

- Protein
- Occult Blood (Hemoglobin)

A further summary will be prepared displaying descriptive statistics of the following parameters in addition to those detailed above:

- Specific Gravity
  - → ≥ 1.000 - < 1.010
  - → ≥ 1.010 - < 1.020
  - → ≥ 1.020

- pH
  - → < 5.0
  - → ≥ 5.0 - < 6.0
  - → ≥ 6.0 - < 7.0
  - → ≥ 7.0 < 8.0
  - → ≥ 8.0

- Bilirubin
- Glucose
- Ketones
- Leukocyte Esterase
- Nitrites
- Urine Erythrocytes
- Urine Leukocytes

All parameters collected from microscopic examination of the sediment (casts, crystals, bacteria, renal tubular epithelial cells, and white blood cells [WBCs]) will be listed only.

Note that screening urinalysis will be locally performed by urine dipstick. Only if dipstick analysis demonstrates high grade proteinuria defined as ≥ 3+ (ie, ≥ 300 mg/dL), will a urine sample be sent to the central laboratory for urinalysis with microscopy. Hence it is expected that the counts for screening be lower than post screening visits in any summaries.

11.10.9 Evaluation of Immunogenic Potential

Immunogenicity testing for serum antibodies to CSL112 and/or apoA-I was performed as a tiered assay suite comprised of screening, confirmatory and titering assays.

A sample with a signal below the cut point in the screening assay was considered negative and a reciprocal titer of 10 was reported.

Any sample with signal above the screening cut point was considered potentially positive and was to be analyzed further using the confirmatory assay.
The confirmatory assay was to follow the same protocol as the screening assay, with the exception of CSL112 being added to detection reagents to demonstrate specificity of signal. If the percent inhibition was below the confirmatory cut point the sample was considered negative and a reciprocal titer of 11 was reported. If a sample had a percent inhibition above the confirmatory cut point it was considered positive and was further tested in the titration assay following an appropriate dilution series. The highest dilution at which the sample result was above the cut point was reported as the reciprocal titer for that sample.

Changes from baseline for these reciprocal titers for serum antibodies to CSL112 and to apoA-I will be summarized by treatment group and a by subject listing provided.

11.11 Other Safety Measures

The denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

11.11.1 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)
- Temperature (^{0}C)
- Weight (kg)

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with Table 3:. The following summaries will be provided:

- Actual and change from baseline by visit
- Incidence of treatment emergent markedly abnormal vital signs
- 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.

11.11.2 ECG

The following ECG parameters will be reported for this study:

- Pulse (bpm)
- PQ/PR Duration (msec)
- RR Interval (msec)
- QRS Duration (msec)
- QT Interval (msec)

- Overall assessment of ECG (Investigator's judgment):
  → Normal
  → Abnormal, Not Clinically Significant (aNCS)
  → Abnormal, Clinically Significant (aCS)

Corrected QT intervals will be derived and reported using the following formulae:

- Bazett's QT correction (QTcB) Interval (msec)

$$\text{QTcB (msec)} = \frac{\text{QT (msec)}}{\sqrt{\text{RR (sec)}}}$$

- Fridericia's QT correction (QTcF) Interval (msec)

$$\text{QTcF (msec)} = \frac{\text{QT (msec)}}{\sqrt[3]{\text{RR (sec)}}}$$

Markedly abnormal quantitative ECG measurements will be identified according to Table 2:. The following summaries will be provided:

- Actual and change from baseline by visit (for quantitative measurements), including the derived QTcB and QTcF values
- Incidence of treatment emergent markedly abnormal ECG intervals
- Shift from baseline to last assessment during Active Treatment Period according to overall assessment (for both quantitative and categorical measurements)
- Listing of all ECG data and of subjects meeting markedly abnormal criteria

11.11.3 Physical Examination

Any abnormal physical examination findings considered by the Investigator as clinically significant at the time of screening will be documented as Medical History. Any clinically significant changes occurring between screening and the end of the study, including drug hypersensitivity findings will be documented in the eCRF as an AE. As a result no summaries or listings will be produced explicitly for physical examinations.

11.12 Treatment Compliance

Subjects will be considered to have received a complete dose of IP, and therefore be compliant, if they have received at least 80% of the IP, and cumulative infusion

interruptions (if any) are for no more than a total of 60 minutes. Compliance to IP will be presented for the SAF.

A summary table showing compliance per infusion and overall, by treatment group will be produced.

Derivation: Proportion of planned IP is derived from data recorded on the IP eCRF page. Proportion of planned IP will be expressed as a percentage and calculated for each infusion separately as;

$$\text{Proportion of Planned IP (\%)} = \frac{\text{Actual Volume of Infusion (mL)} *}{\text{Planned Volume of Infusion (mL)}} \times 100$$

* (including resumed dose following interruption for that infusion)

For the purpose of calculation of the proportion of planned IP infused, any missed infusions will be deemed to have an actual volume of infusion set to 0 mL.

Summaries of the timings between infusions (days) by country and overall will also be produced to investigate adherence to the dosing schedule.

12 Pharmacokinetic Analyses

12.1 Measured and Baseline-Corrected Plasma Apolipoprotein A-I and Phosphatidylcholine Concentrations

Quintiles will produce the following descriptive summaries using the PK Population.

Measured (uncorrected) plasma concentrations and baseline-corrected (change from baseline) concentrations of apoA-I and PC will be listed and summarized by time point, by treatment and by subgroup based on the eGFR (Central) values using central laboratory data.

12.2 Population PK Analysis

A population PK analysis using the PK population will be conducted using a separate analysis plan.

12.3 Deriving and Summarizing Pharmacokinetic Parameters

A summary of the C_{max} and the Accumulation Ratios will be produced. These parameters will be calculated as follows:

Term	Definition
Accumulation Ratio ($R_{A)}$	For subjects receiving CSL112, Accumulation may be obtained using the following accumulation ratio: R_A = Baseline-Corrected End of Infusion$_{Infusion\ 4}$ / Baseline-Corrected End of Infusion$_{Infusion\ 1}$ Note that the Accumulation Ratio will not be calculated for subjects in the Placebo group.
Maximum Concentration ($C_{max)}$	The Maximum Concentration is defined as the End of Infusion concentration after Infusion 1 and Infusion 4. Both baseline-corrected and measured concentrations will be summarized. Note that as concentrations are not measured at regular intervals, the end of infusion concentration will serve as the summary for Maximum Concentration.

13 CCI [redacted]

CCI [redacted]

[redacted]

13.1 CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

13.2 [redacted]

[redacted]

CCI

CCI

13.3

CCI

CCI

13.4

CCI

CCI

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Appendices

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CCI [redacted]	BM	
CCI [redacted]	BM	
CCI [redacted]	BM	
CCI [redacted]	BM	
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CCI [redacted]	BM	
CCI [redacted]	BM	
CCI [redacted]	BM	
CCI [redacted]	BM	
CCI [redacted]	BM	
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CCI	SAF	HLR
CCI	SAF	
CCI	SAF	
CCI	SAF	
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CCI	SAF	
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[redacted]	SAF	
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CCI [redacted]	BM
CCI [redacted]	BM
CCI [redacted]	BM
CCI [redacted]	BM
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13.6 List of Preferred Terms within Standardised MedDRA Queries

13.6.1 Co-Primary Endpoint Renal SAEs

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
Acute Renal Failure, Narrow	20000003	Acute kidney injury	10069339
		Acute phosphate nephropathy	10069688
		Acute prerenal failure	10001017
		Anuria	10002847
		Azotaemia	10003885
		Continuous haemodiafiltration	10066338
		Dialysis	10061105
		Foetal renal impairment	10078987
		Haemodialysis	10018875
		Haemofiltration	10053090
		Hyponatriuria	10077515
		Neonatal anuria	10049778
		Nephropathy toxic	10029155
		Oliguria	10030302
		Peritoneal dialysis	10034660
		Prerenal failure	10072370
		Renal failure	10038435
		Renal failure neonatal	10038447
		Renal impairment	10062237
		Renal impairment neonatal	10049776

13.6.2 Drug Hypersensitivity

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
Hypersensitivity, Narrow	20000214	Acute generalised exanthematous pustulosis	10048799
		Administration site dermatitis	10075096
		Administration site eczema	10075099
		Administration site hypersensitivity	10075102
		Administration site rash	10071156
		Administration site recall reaction	10075964
		Administration site urticaria	10075109
		Administration site vasculitis	10075969
		Allergic bronchitis	10052613
		Allergic colitis	10059447
		Allergic cough	10053779
		Allergic cystitis	10051394
		Allergic eosinophilia	10075185
		Allergic gastroenteritis	10075308
		Allergic hepatitis	10071198
		Allergic keratitis	10057380
		Allergic myocarditis	10001715
		Allergic oedema	10060934
		Allergic otitis externa	10075072
		Allergic otitis media	10061557
		Allergic pharyngitis	10050639
		Allergic reaction to excipient	10078853
		Allergic respiratory disease	10063532
		Allergic respiratory symptom	10063527
		Allergic sinusitis	10049153
		Allergic transfusion reaction	10066173
		Allergy alert test positive	10075479
		Allergy test positive	10056352
		Allergy to immunoglobulin therapy	10074079
		Allergy to surgical sutures	10077279
		Allergy to vaccine	10055048
		Alveolitis allergic	10001890
		Anaphylactic reaction	10002198
		Anaphylactic shock	10002199

		Anaphylactic transfusion reaction	10067113
		Anaphylactoid reaction	10002216
		Anaphylactoid shock	10063119
		Anaphylaxis treatment	10002222
		Angioedema	10002424
		Antiallergic therapy	10064059
		Antiendomysial antibody positive	10065514
		Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894
		Application site dermatitis	10003036
		Application site eczema	10050099
		Application site hypersensitivity	10063683
		Application site rash	10003054
		Application site recall reaction	10076024
		Application site urticaria	10050104
		Application site vasculitis	10076027
		Arthritis allergic	10061430
		Aspirin-exacerbated respiratory disease	10075084
		Atopy	10003645
		Blepharitis allergic	10005149
		Blood immunoglobulin E abnormal	10005589
		Blood immunoglobulin E increased	10005591
		Bromoderma	10006404
		Bronchospasm	10006482
		Catheter site dermatitis	10073992
		Catheter site eczema	10073995
		Catheter site hypersensitivity	10073998
		Catheter site rash	10052271
		Catheter site urticaria	10052272
		Catheter site vasculitis	10074014
		Chronic eosinophilic rhinosinusitis	10071399
		Chronic hyperplastic eosinophilic sinusitis	10071380
		Circulatory collapse	10009192
		Circumoral oedema	10052250
		Conjunctival oedema	10010726
		Conjunctivitis allergic	10010744

		Contact stomatitis	10067510
		Contrast media allergy	10066973
		Contrast media reaction	10010836
		Corneal oedema	10011033
		Cutaneous vasculitis	10011686
		Dennie-Morgan fold	10062918
		Dermatitis	10012431
		Dermatitis acneiform	10012432
		Dermatitis allergic	10012434
		Dermatitis atopic	10012438
		Dermatitis bullous	10012441
		Dermatitis contact	10012442
		Dermatitis exfoliative	10012455
		Dermatitis exfoliative generalised	10012456
		Dermatitis herpetiformis	10012468
		Dermatitis infected	10012470
		Dermatitis psoriasiform	10058675
		Device allergy	10072867
		Dialysis membrane reaction	10076665
		Distributive shock	10070559
		Documented hypersensitivity to administered product	10076470
		Drug cross-reactivity	10076743
		Drug eruption	10013687
		Drug hypersensitivity	10013700
		Drug provocation test	10074350
		Drug reaction with eosinophilia and systemic symptoms	10073508
		Eczema	10014184
		Eczema infantile	10014198
		Eczema nummular	10014201
		Eczema vaccinatum	10066042
		Eczema vesicular	10058681
		Eczema weeping	10055182
		Encephalitis allergic	10056387
		Encephalopathy allergic	10014627

		Eosinophilic granulomatosis with polyangiitis	10078117
		Epidermal necrosis	10059284
		Epidermolysis	10053177
		Epidermolysis bullosa	10014989
		Epiglottic oedema	10015029
		Erythema multiforme	10015218
		Erythema nodosum	10015226
		Exfoliative rash	10064579
		Eye allergy	10015907
		Eye oedema	10052139
		Eye swelling	10015967
		Eyelid oedema	10015993
		Face oedema	10016029
		Fixed eruption	10016741
		Giant papillary conjunctivitis	10018258
		Gingival oedema	10049305
		Gingival swelling	10018291
		Gleich's syndrome	10066837
		Haemorrhagic urticaria	10059499
		Hand dermatitis	10058898
		Henoch-Schonlein purpura	10019617
		Henoch-Schonlein purpura nephritis	10069440
		Heparin-induced thrombocytopenia	10062506
		Hereditary angioedema	10019860
		Hypersensitivity	10020751
		Hypersensitivity vasculitis	10020764
		Idiopathic urticaria	10021247
		Immediate post-injection reaction	10067142
		Immune thrombocytopenic purpura	10074667
		Immune tolerance induction	10070581
		Immune-mediated adverse reaction	10077665
		Implant site dermatitis	10063855
		Implant site hypersensitivity	10063858
		Implant site rash	10063786
		Implant site urticaria	10063787
		Incision site dermatitis	10073168

		Incision site rash	10073411
		Infusion site dermatitis	10065458
		Infusion site eczema	10074850
		Infusion site hypersensitivity	10065471
		Infusion site rash	10059830
		Infusion site recall reaction	10076085
		Infusion site urticaria	10065490
		Infusion site vasculitis	10074851
		Injection site dermatitis	10022056
		Injection site eczema	10066221
		Injection site hypersensitivity	10022071
		Injection site rash	10022094
		Injection site recall reaction	10066797
		Injection site urticaria	10022107
		Injection site vasculitis	10067995
		Instillation site hypersensitivity	10073612
		Instillation site rash	10073622
		Instillation site urticaria	10073627
		Interstitial granulomatous dermatitis	10067972
		Intestinal angioedema	10076229
		Iodine allergy	10052098
		Kaposi's varicelliform eruption	10051891
		Kounis syndrome	10069167
		Laryngeal oedema	10023845
		Laryngitis allergic	10064866
		Laryngospasm	10023891
		Laryngotracheal oedema	10023893
		Limbal swelling	10070492
		Lip oedema	10024558
		Lip swelling	10024570
		Mast cell degranulation present	10076606
		Medical device site dermatitis	10075572
		Medical device site eczema	10075575
		Medical device site hypersensitivity	10075579
		Medical device site rash	10075585
		Medical device site recall reaction	10076140

		Medical device site urticaria	10075588
		Mouth swelling	10075203
		Mucocutaneous rash	10056671
		Multiple allergies	10028164
		Nephritis allergic	10029120
		Nikolsky's sign	10029415
		Nodular rash	10075807
		Oculomucocutaneous syndrome	10030081
		Oculorespiratory syndrome	10067317
		Oedema mouth	10030110
		Oral allergy syndrome	10068355
		Oropharyngeal blistering	10067950
		Oropharyngeal oedema	10078783
		Oropharyngeal spasm	10031111
		Oropharyngeal swelling	10031118
		Palatal oedema	10056998
		Palatal swelling	10074403
		Palisaded neutrophilic granulomatous dermatitis	10068809
		Palpable purpura	10056872
		Pathergy reaction	10074332
		Periorbital oedema	10034545
		Pharyngeal oedema	10034829
		Pruritus allergic	10063438
		Radioallergosorbent test positive	10037789
		Rash	10037844
		Rash erythematous	10037855
		Rash follicular	10037857
		Rash generalised	10037858
		Rash macular	10037867
		Rash maculo-papular	10037868
		Rash maculovesicular	10050004
		Rash morbilliform	10037870
		Rash neonatal	10037871
		Rash papulosquamous	10037879
		Rash pruritic	10037884
		Rash pustular	10037888

		Rash rubelliform	10057984
		Rash scarlatiniform	10037890
		Rash vesicular	10037898
		Reaction to azo-dyes	10037973
		Reaction to colouring	10037974
		Reaction to drug excipients	10064787
		Reaction to preservatives	10064788
		Red man syndrome	10038192
		Rhinitis allergic	10039085
		Scleral oedema	10057431
		Scleritis allergic	10051126
		Scrotal oedema	10039755
		Serum sickness	10040400
		Serum sickness-like reaction	10040402
		Shock	10040560
		Shock symptom	10040581
		Skin necrosis	10040893
		Skin reaction	10040914
		Skin test positive	10040934
		Solar urticaria	10041307
		Solvent sensitivity	10041316
		Stevens-Johnson syndrome	10042033
		Stoma site hypersensitivity	10074509
		Stoma site rash	10059071
		Swelling face	10042682
		Swollen tongue	10042727
		Symmetrical drug-related intertriginous and flexural exanthema	10078325
		Tongue oedema	10043967
		Toxic epidermal necrolysis	10044223
		Toxic skin eruption	10057970
		Tracheal oedema	10044296
		Type I hypersensitivity	10045240
		Type II hypersensitivity	10054000
		Type III immune complex mediated reaction	10053614
		Type IV hypersensitivity reaction	10053613

		Urticaria	10046735
		Urticaria cholinergic	10046740
		Urticaria chronic	10052568
		Urticaria contact	10046742
		Urticaria papular	10046750
		Urticaria physical	10046751
		Urticaria pigmentosa	10046752
		Urticaria vesiculosa	10046755
		Urticarial vasculitis	10048820
		Vaccination site dermatitis	10069477
		Vaccination site eczema	10076161
		Vaccination site exfoliation	10069489
		Vaccination site hypersensitivity	10068880
		Vaccination site rash	10069482
		Vaccination site recall reaction	10076188
		Vaccination site urticaria	10069622
		Vaccination site vasculitis	10076191
		Vaccination site vesicles	10069623
		Vaginal exfoliation	10064483
		Vaginal ulceration	10046943
		Vasculitic rash	10047111
		Vessel puncture site rash	10077117
		Vessel puncture site vesicles	10077813
		Vulval ulceration	10047768
		Vulvovaginal rash	10071588
		Vulvovaginal ulceration	10050181

13.6.3 **Bleeding Events**

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
Haemorrhage Terms (excl laboratory terms), Narrow	20000039	Abdominal wall haematoma	10067383
		Abdominal wall haemorrhage	10067788
		Abnormal withdrawal bleeding	10069195
		Acute haemorrhagic leukoencephalitis	10058994
		Acute haemorrhagic ulcerative colitis	10075634
		Administration site bruise	10075094
		Administration site haematoma	10075100
		Administration site haemorrhage	10075101
		Adrenal haematoma	10059194
		Adrenal haemorrhage	10001361
		Anal haemorrhage	10049555
		Anal ulcer haemorrhage	10063896
		Anastomotic haemorrhage	10056346
		Anastomotic ulcer haemorrhage	10002244
		Aneurysm ruptured	10048380
		Angina bullosa haemorrhagica	10064223
		Anorectal varices haemorrhage	10068925
		Aortic aneurysm rupture	10002886
		Aortic dissection rupture	10068119
		Aortic intramural haematoma	10067975
		Aortic perforation	10075729
		Aortic rupture	10060874
		Aponeurosis contusion	10075330
		Application site bruise	10050114
		Application site haematoma	10068317
		Application site haemorrhage	10072694
		Application site purpura	10050182
		Arterial haemorrhage	10060964
		Arterial intramural haematoma	10074971
		Arterial perforation	10075732
		Arterial rupture	10003173
		Arteriovenous fistula site haematoma	10055150
		Arteriovenous fistula site haemorrhage	10055123
		Arteriovenous graft site haematoma	10055152
		Arteriovenous graft site haemorrhage	10055126

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Astringent therapy	10067372
		Atrial rupture	10048761
		Auricular haematoma	10003797
		Basal ganglia haematoma	10077031
		Basal ganglia haemorrhage	10067057
		Basilar artery perforation	10075736
		Bladder tamponade	10062656
		Bleeding varicose vein	10005144
		Blood blister	10005372
		Blood urine	10005863
		Blood urine present	10018870
		Bloody discharge	10057687
		Bloody peritoneal effluent	10067442
		Bone contusion	10066251
		Bone marrow haemorrhage	10073581
		Brain contusion	10052346
		Brain stem haematoma	10073230
		Brain stem haemorrhage	10006145
		Brain stem microhaemorrhage	10071205
		Breast haematoma	10064753
		Breast haemorrhage	10006254
		Broad ligament haematoma	10006375
		Bronchial haemorrhage	10065739
		Bronchial varices haemorrhage	10079163
		Bursal haematoma	10077818
		Cardiac contusion	10073356
		Carotid aneurysm rupture	10051328
		Carotid artery perforation	10075728
		Catheter site bruise	10063587
		Catheter site haematoma	10055662
		Catheter site haemorrhage	10051099
		Central nervous system haemorrhage	10072043
		Cephalhaematoma	10008014
		Cerebellar haematoma	10061038
		Cerebellar haemorrhage	10008030
		Cerebellar microhaemorrhage	10071206
		Cerebral aneurysm perforation	10075394

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Cerebral aneurysm ruptured syphilitic	10008076
		Cerebral arteriovenous malformation haemorrhagic	10008086
		Cerebral artery perforation	10075734
		Cerebral haematoma	10053942
		Cerebral haemorrhage	10008111
		Cerebral haemorrhage foetal	10050157
		Cerebral haemorrhage neonatal	10008112
		Cerebral microhaemorrhage	10067277
		Cervix haematoma uterine	10050020
		Cervix haemorrhage uterine	10050022
		Chest wall haematoma	10076597
		Choroidal haematoma	10068642
		Choroidal haemorrhage	10008786
		Chronic gastrointestinal bleeding	10050399
		Chronic pigmented purpura	10072726
		Ciliary body haemorrhage	10057417
		Coital bleeding	10065019
		Colonic haematoma	10009996
		Conjunctival haemorrhage	10010719
		Contusion	10050584
		Corneal bleeding	10051558
		Cullen's sign	10059029
		Cystitis haemorrhagic	10011793
		Deep dissecting haematoma	10074718
		Diarrhoea haemorrhagic	10012741
		Disseminated intravascular coagulation	10013442
		Diverticulitis intestinal haemorrhagic	10013541
		Diverticulum intestinal haemorrhagic	10013560
		Duodenal ulcer haemorrhage	10013839
		Duodenitis haemorrhagic	10013865
		Dysfunctional uterine bleeding	10013908
		Ear haemorrhage	10014009
		Ecchymosis	10014080
		Encephalitis haemorrhagic	10014589
		Enterocolitis haemorrhagic	10014896
		Epidural haemorrhage	10073681
		Epistaxis	10015090

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Exsanguination	10015719
		Extra-axial haemorrhage	10078254
		Extradural haematoma	10015769
		Extravasation blood	10015867
		Eye contusion	10073354
		Eye haemorrhage	10015926
		Eyelid bleeding	10053196
		Eyelid contusion	10075018
		Eyelid haematoma	10064976
		Femoral artery perforation	10075739
		Femoral vein perforation	10075745
		Foetal-maternal haemorrhage	10016871
		Gastric haemorrhage	10017788
		Gastric ulcer haemorrhage	10017826
		Gastric ulcer haemorrhage, obstructive	10017829
		Gastric varices haemorrhage	10057572
		Gastritis alcoholic haemorrhagic	10017857
		Gastritis haemorrhagic	10017866
		Gastroduodenal haemorrhage	10053768
		Gastroduodenitis haemorrhagic	10048712
		Gastrointestinal angiodysplasia haemorrhagic	10017929
		Gastrointestinal haemorrhage	10017955
		Gastrointestinal polyp haemorrhage	10074437
		Gastrointestinal ulcer haemorrhage	10056743
		Genital contusion	10073355
		Genital haemorrhage	10061178
		Gingival bleeding	10018276
		Graft haemorrhage	10063577
		Grey Turner's sign	10075426
		Haemarthrosis	10018829
		Haematemesis	10018830
		Haematochezia	10018836
		Haematocoele	10018833
		Haematoma	10018852
		Haematoma evacuation	10060733
		Haematoma infection	10051564
		Haematosalpinx	10050468

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Haematospermia	10018866
		Haematotympanum	10063013
		Haematuria	10018867
		Haematuria traumatic	10018871
		Haemobilia	10058947
		Haemophilic arthropathy	10065057
		Haemoptysis	10018964
		Haemorrhage	10055798
		Haemorrhage coronary artery	10055803
		Haemorrhage foetal	10061191
		Haemorrhage in pregnancy	10018981
		Haemorrhage intracranial	10018985
		Haemorrhage neonatal	10061993
		Haemorrhage subcutaneous	10018999
		Haemorrhage subepidermal	10019001
		Haemorrhage urinary tract	10055847
		Haemorrhagic anaemia	10052293
		Haemorrhagic arteriovenous malformation	10064595
		Haemorrhagic ascites	10059766
		Haemorrhagic breast cyst	10077443
		Haemorrhagic cerebral infarction	10019005
		Haemorrhagic cyst	10059189
		Haemorrhagic diathesis	10062713
		Haemorrhagic disease of newborn	10019008
		Haemorrhagic disorder	10019009
		Haemorrhagic erosive gastritis	10067786
		Haemorrhagic hepatic cyst	10067796
		Haemorrhagic infarction	10019013
		Haemorrhagic necrotic pancreatitis	10076058
		Haemorrhagic ovarian cyst	10060781
		Haemorrhagic stroke	10019016
		Haemorrhagic thyroid cyst	10072256
		Haemorrhagic transformation stroke	10055677
		Haemorrhagic tumour necrosis	10054096
		Haemorrhagic urticaria	10059499
		Haemorrhagic vasculitis	10071252
		Haemorrhoidal haemorrhage	10054787

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Haemostasis	10067439
		Haemothorax	10019027
		Henoch-Schonlein purpura	10019617
		Hepatic haemangioma rupture	10054885
		Hepatic haematoma	10019676
		Hepatic haemorrhage	10019677
		Hereditary haemorrhagic telangiectasia	10019883
		Hyperfibrinolysis	10074737
		Hyphaema	10020923
		Iliac artery perforation	10075731
		Iliac artery rupture	10072789
		Iliac vein perforation	10075744
		Immune thrombocytopenic purpura	10074667
		Implant site bruising	10063850
		Implant site haematoma	10063780
		Implant site haemorrhage	10053995
		Incision site haematoma	10059241
		Incision site haemorrhage	10051100
		Increased tendency to bruise	10021688
		Induced abortion haemorrhage	10052844
		Inferior vena cava perforation	10075742
		Infusion site bruising	10059203
		Infusion site haematoma	10065463
		Infusion site haemorrhage	10065464
		Injection site bruising	10022052
		Injection site haematoma	10022066
		Injection site haemorrhage	10022067
		Instillation site bruise	10073630
		Instillation site haematoma	10073609
		Instillation site haemorrhage	10073610
		Internal haemorrhage	10075192
		Intestinal haematoma	10069829
		Intestinal haemorrhage	10059175
		Intestinal varices haemorrhage	10078058
		Intra-abdominal haematoma	10056457
		Intra-abdominal haemorrhage	10061249
		Intracerebral haematoma evacuation	10062025

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Intracranial haematoma	10059491
		Intracranial tumour haemorrhage	10022775
		Intraocular haematoma	10071934
		Intrapartum haemorrhage	10067703
		Intraventricular haemorrhage	10022840
		Intraventricular haemorrhage neonatal	10022841
		Iris haemorrhage	10057418
		Joint microhaemorrhage	10077666
		Kidney contusion	10023413
		Lacrimal haemorrhage	10069930
		Large intestinal haemorrhage	10052534
		Large intestinal ulcer haemorrhage	10061262
		Laryngeal haematoma	10070885
		Laryngeal haemorrhage	10065740
		Lip haematoma	10066304
		Lip haemorrhage	10049297
		Liver contusion	10067266
		Lower gastrointestinal haemorrhage	10050953
		Lower limb artery perforation	10075730
		Lymph node haemorrhage	10074270
		Mallory-Weiss syndrome	10026712
		Mediastinal haematoma	10049941
		Mediastinal haemorrhage	10056343
		Medical device site bruise	10075570
		Medical device site haematoma	10075577
		Medical device site haemorrhage	10075578
		Melaena	10027141
		Melaena neonatal	10049777
		Meningorrhagia	10052593
		Menometrorrhagia	10027295
		Menorrhagia	10027313
		Mesenteric haematoma	10071557
		Mesenteric haemorrhage	10060717
		Metrorrhagia	10027514
		Mouth haemorrhage	10028024
		Mucocutaneous haemorrhage	10076048
		Mucosal haemorrhage	10061298

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Muscle contusion	10070757
		Muscle haemorrhage	10028309
		Myocardial haemorrhage	10048849
		Myocardial rupture	10028604
		Naevus haemorrhage	10062955
		Nail bed bleeding	10048891
		Nasal septum haematoma	10075027
		Neonatal gastrointestinal haemorrhage	10074159
		Nephritis haemorrhagic	10029132
		Nipple exudate bloody	10029418
		Ocular retrobulbar haemorrhage	10057571
		Oesophageal haemorrhage	10030172
		Oesophageal intramural haematoma	10077486
		Oesophageal ulcer haemorrhage	10030202
		Oesophageal varices haemorrhage	10030210
		Oesophagitis haemorrhagic	10030219
		Optic disc haemorrhage	10030919
		Optic nerve sheath haemorrhage	10030941
		Oral contusion	10078170
		Oral mucosa haematoma	10074779
		Osteorrhagia	10051937
		Ovarian haematoma	10033263
		Ovarian haemorrhage	10065741
		Palpable purpura	10056872
		Pancreatic haemorrhage	10033625
		Pancreatitis haemorrhagic	10033650
		Papillary muscle haemorrhage	10059164
		Paranasal sinus haematoma	10069702
		Parathyroid haemorrhage	10059051
		Parotid gland haemorrhage	10051166
		Pelvic haematoma	10054974
		Pelvic haematoma obstetric	10034248
		Pelvic haemorrhage	10063678
		Penile contusion	10073352
		Penile haematoma	10070656
		Penile haemorrhage	10034305
		Peptic ulcer haemorrhage	10034344

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Pericardial haemorrhage	10034476
		Perineal haematoma	10034520
		Periorbital haematoma	10034544
		Periorbital haemorrhage	10071697
		Periosteal haematoma	10077341
		Peripartum haemorrhage	10072693
		Perirenal haematoma	10049450
		Peritoneal haematoma	10058095
		Peritoneal haemorrhage	10034666
		Periventricular haemorrhage neonatal	10076706
		Petechiae	10034754
		Pharyngeal haematoma	10068121
		Pharyngeal haemorrhage	10034827
		Pituitary haemorrhage	10049760
		Placenta praevia haemorrhage	10035121
		Polymenorrhagia	10064050
		Post abortion haemorrhage	10036246
		Post procedural contusion	10073353
		Post procedural haematoma	10063188
		Post procedural haematuria	10066225
		Post procedural haemorrhage	10051077
		Post transfusion purpura	10072265
		Postmenopausal haemorrhage	10055870
		Postpartum haemorrhage	10036417
		Post-traumatic punctate intraepidermal haemorrhage	10071639
		Premature separation of placenta	10036608
		Procedural haemorrhage	10071229
		Proctitis haemorrhagic	10036778
		Prostatic haemorrhage	10036960
		Pulmonary alveolar haemorrhage	10037313
		Pulmonary contusion	10037370
		Pulmonary haematoma	10054991
		Pulmonary haemorrhage	10037394
		Puncture site haemorrhage	10051101
		Purpura	10037549
		Purpura fulminans	10037556
		Purpura neonatal	10037557

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Purpura non-thrombocytopenic	10057739
		Purpura senile	10037560
		Putamen haemorrhage	10058940
		Radiation associated haemorrhage	10072281
		Rectal haemorrhage	10038063
		Rectal ulcer haemorrhage	10038081
		Renal artery perforation	10075737
		Renal cyst haemorrhage	10059846
		Renal haematoma	10038459
		Renal haemorrhage	10038460
		Respiratory tract haemorrhage	10038727
		Respiratory tract haemorrhage neonatal	10038728
		Retinal aneurysm rupture	10079121
		Retinal haemorrhage	10038867
		Retinopathy haemorrhagic	10051447
		Retroperitoneal haematoma	10058360
		Retroperitoneal haemorrhage	10038980
		Retroplacental haematoma	10054798
		Ruptured cerebral aneurysm	10039330
		Scleral haemorrhage	10050508
		Scrotal haematocoele	10061517
		Scrotal haematoma	10039749
		Shock haemorrhagic	10049771
		Skin haemorrhage	10064265
		Skin neoplasm bleeding	10060712
		Skin ulcer haemorrhage	10050377
		Small intestinal haemorrhage	10052535
		Small intestinal ulcer haemorrhage	10061550
		Soft tissue haemorrhage	10051297
		Spermatic cord haemorrhage	10065742
		Spinal cord haematoma	10076051
		Spinal cord haemorrhage	10048992
		Spinal epidural haematoma	10050162
		Spinal epidural haemorrhage	10049236
		Spinal subarachnoid haemorrhage	10073564
		Spinal subdural haematoma	10050164
		Spinal subdural haemorrhage	10073563

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Spleen contusion	10073533
		Splenic artery perforation	10075738
		Splenic haematoma	10041646
		Splenic haemorrhage	10041647
		Splenic varices haemorrhage	10068662
		Splinter haemorrhages	10041663
		Spontaneous haematoma	10065304
		Spontaneous haemorrhage	10074557
		Stoma site haemorrhage	10074508
		Stomatitis haemorrhagic	10042132
		Subarachnoid haematoma	10076701
		Subarachnoid haemorrhage	10042316
		Subarachnoid haemorrhage neonatal	10042317
		Subchorionic haematoma	10072596
		Subchorionic haemorrhage	10071010
		Subclavian artery perforation	10075740
		Subclavian vein perforation	10075743
		Subcutaneous haematoma	10042345
		Subdural haematoma	10042361
		Subdural haematoma evacuation	10042363
		Subdural haemorrhage	10042364
		Subdural haemorrhage neonatal	10042365
		Subgaleal haematoma	10069510
		Subretinal haematoma	10071935
		Superior vena cava perforation	10075741
		Testicular haemorrhage	10051877
		Thalamus haemorrhage	10058939
		Third stage postpartum haemorrhage	10043449
		Thoracic haemorrhage	10062744
		Thrombocytopenic purpura	10043561
		Thrombotic thrombocytopenic purpura	10043648
		Thyroid haemorrhage	10064224
		Tongue haematoma	10043959
		Tongue haemorrhage	10049870
		Tonsillar haemorrhage	10057450
		Tooth pulp haemorrhage	10072228
		Tooth socket haemorrhage	10064946

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Tracheal haemorrhage	10062543
		Traumatic haematoma	10044522
		Traumatic haemorrhage	10053476
		Traumatic haemothorax	10074487
		Traumatic intracranial haematoma	10079013
		Traumatic intracranial haemorrhage	10061387
		Tumour haemorrhage	10049750
		Ulcer haemorrhage	10061577
		Umbilical cord haemorrhage	10064534
		Umbilical haematoma	10068712
		Umbilical haemorrhage	10045455
		Upper gastrointestinal haemorrhage	10046274
		Ureteric haemorrhage	10065743
		Urethral haemorrhage	10049710
		Urinary bladder haemorrhage	10046528
		Urogenital haemorrhage	10050058
		Uterine haematoma	10063875
		Uterine haemorrhage	10046788
		Vaccination site bruising	10069484
		Vaccination site haematoma	10069472
		Vaccination site haemorrhage	10069475
		Vaginal haematoma	10046909
		Vaginal haemorrhage	10046910
		Varicose vein ruptured	10046999
		Vascular access site bruising	10077767
		Vascular access site haematoma	10077647
		Vascular access site haemorrhage	10077643
		Vascular access site rupture	10077652
		Vascular graft haemorrhage	10077721
		Vascular pseudoaneurysm ruptured	10053949
		Vascular purpura	10047097
		Vascular rupture	10053649
		Vein rupture	10077110
		Venous haemorrhage	10065441
		Venous perforation	10075733
		Ventricle rupture	10047279
		Vertebral artery perforation	10075735

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
		Vessel puncture site bruise	10063881
		Vessel puncture site haematoma	10065902
		Vessel puncture site haemorrhage	10054092
		Vitreous haematoma	10071936
		Vitreous haemorrhage	10047655
		Vulval haematoma	10047756
		Vulval haematoma evacuation	10047757
		Vulval haemorrhage	10063816
		Withdrawal bleed	10047998
		Wound haematoma	10071504
		Wound haemorrhage	10051373

13.6.4 Hemolysis

MedDRA v20.0 SMQ	SMQ Code	PT	PT Code
Haemolytic Disorders, Narrow	20000019	ABO haemolytic disease of newborn	10000205
		ABO incompatibility	10000206
		Acid haemolysin test positive	10073783
		Acute haemolytic transfusion reaction	10066181
		Alloimmunisation	10060935
		Anti A antibody positive	10074302
		Anti B antibody positive	10074303
		Anti Kell antibody test positive	10078305
		Anti-erythrocyte antibody positive	10057108
		Autoimmune haemolytic anaemia	10073785
		Blood incompatibility haemolytic anaemia of newborn	10056369
		Cardiac haemolytic anaemia	10072202
		Cold agglutinins positive	10009854
		Cold type haemolytic anaemia	10009868
		Coombs direct test positive	10010933
		Coombs indirect test positive	10010938
		Coombs negative haemolytic anaemia	10010940
		Coombs positive haemolytic anaemia	10010941
		Coombs test positive	10061090
		Delayed haemolytic transfusion reaction	10066182
		Erythroblastosis	10049466
		Erythroblastosis foetalis	10015251
		Evans syndrome	10053873
		Extravascular haemolysis	10015871
		Glucose-6-phosphate dehydrogenase abnormal	10059902
		Glucose-6-phosphate dehydrogenase deficiency	10018444
		Haemoglobin urine present	10018909
		Haemoglobinaemia	10018901
		Haemoglobinuria	10018906
		Haemolysis	10018910
		Haemolysis neonatal	10050190
		Haemolytic anaemia	10018916
		Haemolytic transfusion reaction	10067122
		Haemolytic uraemic syndrome	10018932
		Haemosiderinuria	10069395

		Haptoglobin decreased	10019150
		Intravascular haemolysis	10022822
		Isoimmune haemolytic disease	10023052
		Jaundice acholuric	10023128
		Microangiopathic haemolytic anaemia	10027527
		Paroxysmal nocturnal haemoglobinuria	10034042
		Passenger lymphocyte syndrome	10073596
		Red cell fragmentation syndrome	10072203
		Rhesus antibodies positive	10039036
		Rhesus haemolytic disease of newborn	10039037
		Rhesus incompatibility	10063676
		Schistocytosis	10076534
		Transfusion reaction	10044359
		Warm type haemolytic anaemia	10047822

13.7 Source Data for Identifying Baseline Medications of Interest

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