STATISTICAL ANALYSIS PLAN (SAP)

Study Title: A Phase 2a, Double-blind, Randomized, Placebo-controlled, Proof of Concept Study of Vascular Endothelial Growth Factor (VEGF)-B Blockade with the Monoclonal Antibody CSL346 in Subjects with Diabetic Kidney Disease

Study Number:	CSL346_2001
Study Product:	CSL346
Development Phase:	2a
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Version:	Final 3.0
Version Date:	29Sep2022
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

COMMERCIAL IN CONFIDENCE

Table of Contents

List of Tables

List of Figures

1 Modification History

Version	Effective Date	Author of Modification	Summary of Change
Draft 1.0	30Sep2020	PPD	N/A – First Version
Draft 2.0	28Oct2020	PPD	Implementation of sponsor review comments
Draft 3.0	07Dec2020	PPD	Implementation of sponsor review comments
Final 1.0	11Dec2020	PPD	N/A
Draft of Final 1.1	16Jul2021	PPD	Alignment with Protocol Amendment 2 including; • Added potential inclusion of subjects with estimated glomerular filtration rate between > 20 and < 45 mL/min/1.73m2 subject to endorsement by the Independent Data Monitoring Committee • Changed the adverse events of special interest criteria for increases in albumin-to-creatinine ratio • Added sensitivity analysis employing multiple imputation for missing data • Added sensitivity analysis to reflect the impact of novel coronavirus 2019 • Added Screened Analysis Set • Added Interim Analysis for decision making
Draft of Final 1.2	02Dec2021	PPD	Implementation of sponsor review comments for alignment with Protocol Amendment 2

Version	Effective Date	Author of Modification	Summary of Change
Final 2.0	10Dec2021	PPD	N/A
Final 3.0	29Sep2022	PPD	• Summaries of Prior and Concomitant medications will be based on either the Safety Analysis Set or the Per Protocol Analysis Set. • Added Appendix table showing directionality of one-sided testing • Clarification regarding normalization of urinary biomarkers • Specification of non-SI units for particular parameter reporting • Correction of estimand • Clarifications and updates regarding Per Protocol Analysis Set • Baseline for multiple parameters defined as the average of two measurements • Sentence added indicating total dose received (mg/kg) will be provided with study data • Specification for KIM-1, NGAL, EGF (new parameter), and MCP-1 analyses to be performed for the PP Analysis Set • Removal of VEGF-B since it will not be available

2 List of Abbreviations

Abbreviation	Term
ACR	Albumin to creatinine ratio
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
AKI	Acute Kidney Injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BLQ	Below level of quantification
BMI	Body mass index
BP	Blood Pressure
CI	Confidence interval
CDISC	Clinical Data Interchange Standards Consortium
CTMS	Clinical Trail Management System
CV	Coefficient of Variation
DBL	Database lock
DBP	Diastolic blood pressure
DKD	Diabetic Kidney Disease
ECG	Electrocardiogram
EDC	Electronic data capture
EGF	Epidermal growth factor
EOS	End of study
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FMV	First morning void
HbA1c	hemoglobin A1c
HDL	High density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee

Abbreviation	Term
IP	Investigational product
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
KIM-1	Kidney injury molecule-1
LDL	Low density lipoprotein
LLN	Lower limit of the normal
LVEF	Left ventricular ejection fraction
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model repeated measures
NC	Not calculated
NEFA	Non-esterified fatty acids
NGAL	Neutrophil gelatinase-associated lipocalin
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred term
QTcB	Corrected QT interval (Bazett's formula)
QTcF	Corrected QT interval (Fridericia's formula)
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SBP	Systolic blood pressure
SCr	Serum creatinine
SDG	Standardized Drug Grouping
SEM	Standard error of the mean
SGLT2i	Sodium-glucose cotransporter 2 inhibitor
SC	Subcutaneous
SD	Standard Deviation

Abbreviation	Term
SDTM	Study Data Tabulation Model
SMQ	Standard MedDRA Query
SOC	System organ class
sTNFR1	soluble tumor necrosis factor receptor 1
T2DM	Type II diabetes mellitus
TEAE	Treatment Emergent Adverse Event
TFL	Tables, figures, and listings
ULN	Upper limit of the normal
WHO	World Health Organization
VEGF-B	Vascular Endothelial Growth Factor Bd
VEGF-R1	soluble VEGF receptor 1

3 Purpose

This statistical analysis plan (SAP) provides a detailed and complete description of the planned final analysis for the study CSL346_2001. Mock table, figure, and listing (TFL) shells will be provided in a separate supporting document along with details for the practical implementation of the analyses.

This SAP complies with the International Council for Harmonisation (ICH) E9 ‘Statistical Principles for Clinical Trials’ and E9 (R1) ‘Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials’. It is based upon the following study documents:

- Study Protocol (dated 16 Jan 2020);
- Study Protocol Amendment 1 (dated 07 May 2020);
- Study Protocol Amendment 2 (dated 27 May 2021);
- Protocol Deviation Plan (dated 04 Sep 2020);
- Case Report Form (CRF), Version 1.0 (dated 28 Aug 2020).

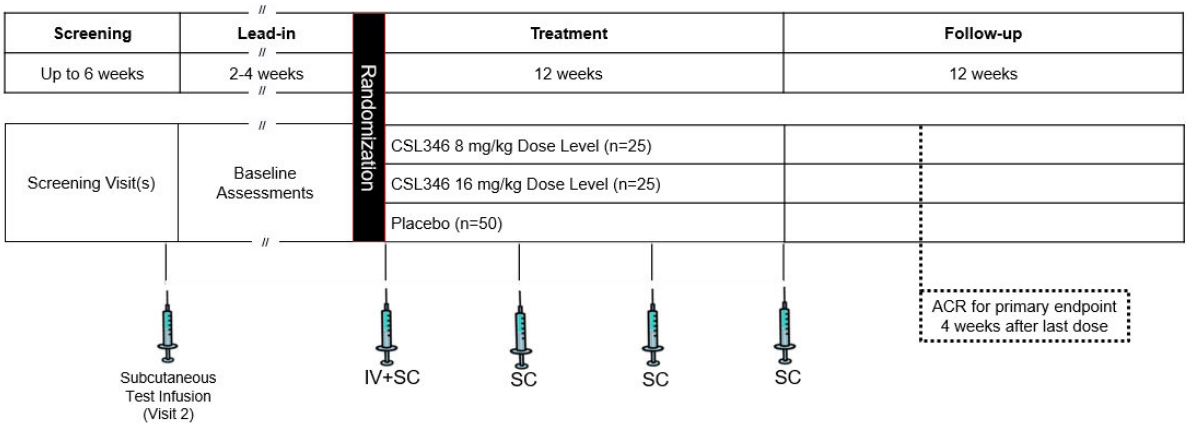
All decisions regarding the analysis of the study results, as defined in this version of the SAP, have been made before database lock (DBL) of the study data.

Deviations from the analyses in this SAP will be detailed in the clinical study report (CSR).

4 Study Design

This is a prospective, multicenter, randomized, double-blind, placebo-controlled, proof of concept study to investigate the efficacy, safety, tolerability, and pharmacokinetics (PK) of repeat doses of CSL346 in 100 subjects with diabetic kidney disease (DKD) and albuminuria receiving standard of care treatment. The study will be divided into 4 periods: Screening, Lead-in, Treatment, and Follow-up, as shown in the following schematic:

Figure 1 Study Design Overview



Screening Period

The Screening Period begins with the completion of the informed consent process and includes up to 6 weeks for determination of subject eligibility. During Screening (Visit 1 and Visit 2), the investigator or delegate will assess the subject's eligibility for the study according to Inclusion / Exclusion Criteria. A subcutaneous (SC) test infusion is to be done at Visit 2 after other subject eligibility criteria have been confirmed.

Lead-in Period

During the Lead-in Period, subjects will have a study visit approximately 1 week before randomization (Visit 3, Day –7 ± 4 days). The subject's eligibility to continue into the Treatment Period will be assessed according to Randomization Criteria.

Treatment Period

The Treatment Period will include up to 12 weeks of approximately monthly (every 4 weeks) administration of investigational product (IP). Using an Interactive Response Technology (IRT) system, eligible subjects will be randomized (1:1:2) to receive blinded IP (8 mg/kg CSL346, 16 mg/kg CSL346, or placebo). Randomization will be stratified by whether the subjects are receiving a concomitant sodium-glucose cotransporter 2 inhibitor (SGLT2i). At least half of the population should be receiving an SGLT2i.

Each subject's first dose of IP at Visit 4 (Day 1) will be an intravenous (IV) loading dose of 3 mg/kg CSL346 for subjects randomized to 8 mg/kg CSL346 and 6 mg/kg CSL346 for subjects randomized to 16 mg/kg CSL346, or placebo (subjects randomized to placebo). The subject's first SC dose of IP will be administered as 8 mg/kg, 16 mg/kg, or placebo, respectively. Subjects will receive 3 subsequent SC infusions at Visit 7 (Week 4), Visit 8 (Week 8), and Visit 9 (Week 12) for a total of 4 SC doses.

Follow-up Period

The Follow-up Period will continue for 12 weeks after the subject's last dose of IP to evaluate changes in safety, efficacy, PK, and pharmacodynamic (PD) parameters after stopping treatment.

4.1 Objectives and Endpoints

4.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of CSL346 administered every 4 weeks for up to 12 weeks (4 doses) in subjects with DKD.

4.1.2 Secondary Objectives

The secondary objectives of this study are:

1. To evaluate the safety and tolerability of CSL346 administered every 4 weeks for up to 12 weeks (4 doses) in subjects with DKD.
2. To evaluate the effect of CSL346 on serum creatinine (SCr) concentration and estimated glomerular filtration rate (eGFR) in subjects with DKD.
3. To evaluate the effect of CSL346 on blood pressure (BP) in subjects with DKD.
4. To evaluate the PK of CSL346 in subjects with DKD.
5. To evaluate the immunogenicity of CSL346 in subjects with DKD.

4.1.3 Exploratory Objectives

The exploratory objectives of this study are:

1. To explore the effect of CSL346 on the following potential PD biomarkers:
   - biomarkers of lipid metabolism;
   - biomarkers of glycemic control;
   - novel plasma, serum and urinary biomarkers.
2. To measure the concentration of CSL346 in the urine and explore its association with albuminuria.
3. To explore the relationship between PD biomarkers and CSL346 PK characteristics.

4. To evaluate the frequency of subjects with macroalbuminuria (albumin to creatinine ratio (ACR) > 300 mg/g [33.9 mg/mmol]) at Baseline regressing to microalbuminuria (ACR > 30 and ≤ 300 mg/g [> 3.39 and ≤ 33.9 mg/mmol]) or normoalbuminuria (ACR ≤ 30 mg/g [3.39 mg/mmol]), or from microalbuminuria to normoalbuminuria.
5. To explore possible dose response for the primary and secondary efficacy and safety endpoints.

4.1.4 Exploratory Endpoints

The exploratory endpoints for this study are:

1. Changes from Baseline to each assessment in fasting values for the following PD biomarkers:
   - biomarkers of lipid metabolism including but not limited to circulating total cholesterol, triglycerides, high density lipoproteins (HDL), low density lipoproteins (LDL), glycerol, non-esterified fatty acids (NEFA), and ketones;
   - biomarkers of glycemic control including but not limited to fasting glucose and hemoglobin A1c (HbA1c);
   - novel biomarkers, including but not limited to soluble tumor necrosis factor receptor 1 (sTNFR1), and urinary VEGF-A, soluble VEGF receptor 1 (VEGF-R1), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), epidermal growth factor (EGF), clusterin, and monocyte chemoattractant protein-1 (MCP-1).
2. Concentration of CSL346 found in urine at Week 1 (Visit 5) and Week 12 (Visit 9).
3. Number (percent) of patients who regress from macroalbuminuria to microalbuminuria or normoalbuminuria, or from microalbuminuria to normoalbuminuria at Week 16 (Visit 10) compared to Baseline.

Table 1 Study Objectives, Endpoints and Summary Measures

Objectives	Endpoints	Summary Measure(s)
Primary	Change in log-transformed urinary albumin-to-creatinine ratio (ACR) from Baseline to Week 16 (Visit 10)	Geometric mean ratio for CSL346 (8 mg/kg and 16 mg/kg combined) versus placebo (80% confidence interval CI), expressed as percent change from Baseline
Key Secondary	Treatment-emergent adverse events (TEAEs), including adverse events of special interest (AESIs) from the time of first dose of IP through End of Study (EOS)	Number and percentage of subjects overall, by severity, by relatedness, by seriousness, and by action (i.e. IP discontinuation)
	Observed value and change from Baseline in SCr and eGFR through EOS	Mean (standard deviation (SD))
Other Secondary	Observed value and change from Baseline in systolic and diastolic blood pressure (SBP and DBP) through EOS	Mean (SD)
	CSL346 serum PK: Maximum concentration (C_{max}) after IV loading dose Time to reach C_{max} in serum (T_{max}) after IV loading dose C_{max} after first SC dose T_{max} in serum after first SC dose Area under the concentration-time curve in first dosing interval ($AUC_{0-\tau}$) C_{trough} after each dose	Mean (SD), coefficient of variation (% CV) and geometric mean for all parameters except T_{max}; Median (minimum, maximum) for T_{max}
	Presence of Anti-Drug Antibody (ADA) at Week 4 (Visit 7), Week 8 (Visit 8), and Week 16 (Visit 10)	Number and percentage of subjects with positive result (with reciprocal titer)

Objectives	Endpoints	Summary Measure(s)
Exploratory	Changes from Baseline to each assessment in fasting values for PD biomarkers	Mean (SD)
	Concentration of CSL346 found in urine at Week 1 (Visit 5) and Week 12 (Visit 9)	Mean (SD)
	Number (percent) of patients who regress from macroalbuminuria to microalbuminuria or normoalbuminuria, or from microalbuminuria to normoalbuminuria at Week 16 (Visit 10) compared to Baseline	Number and percentage of subjects

4.1.5 Primary Study Hypotheses

The primary study hypothesis is that the ACR geometric mean ratio for CSL346 (8 mg/kg and 16 mg/kg combined) versus placebo (80% CI) at 16 weeks is less than 1. The test for superiority will be conducted at the one-sided, 0.10 alpha level.

Hypotheses will be tested using a one-sided test at α=0.10:

H0: GMR >= 1.0 vs. H1: GMR < 1.0

(i.e. $GMR = \frac{0.5*(\text{CSL346}\frac{8\text{mg}}{\text{kg}} + \text{CSL346}\frac{16\text{mg}}{\text{kg}})}{Placebo}$),

where GMR is the geometric mean ratio of the change from baseline in albumin/creatinine ratio.

4.1.6 Key Secondary Study Hypotheses

The key secondary hypothesis regarding decreases in serum creatinine, blood pressure (SBP and DBP) and eGFR will be conducted in a similar manner as for the primary study hypothesis, but using mean instead of geometric mean.

4.2 Study Treatments

CSL346 will be administered at an initial IV loading dose of 3 mg/kg or 6 mg/kg IV in the arm, followed by 8 mg/kg or 16 mg/kg SC, respectively, in the abdomen at least 2 hours but

no more than 6 hours later. Subsequent SC infusions (8 mg/kg or 16 mg/kg per dose) will be administered every 4 weeks for 12 weeks.

All doses of IP will be administered by IV or SC infusion at the study site. Subjects will be considered to have received a complete dose of IP if they receive at least 80% of IP. Subjects experiencing a mild local injection site reaction deemed unacceptable by the subject or investigator may have administration and / or dose adjustments.

Eligible subjects will be randomized by means of IRT. The IRT will assign the IP to each subject. Randomization will be done centrally. Subjects will be stratified by whether subjects are receiving concomitant treatment with an SGLT2i. More details can be found in the clinical study protocol.

4.3 Randomization Procedures and Blinding

Eligible subjects will be randomized by means of IRT in a 1:1:2 ratio to CSL346 8mg/kg, CSL346 16 mg/kg and placebo, respectively. Investigational product will be prepared by the unblinded site pharmacist (or other dedicated unblinded site personnel) and blinded for administration to study subjects. IV loading doses and SC doses of CSL346 and placebo will appear identical to site staff and subjects. Randomization will be done centrally. Subjects will be stratified by concomitant use of SGLT2is. More details can be found in the clinical study protocol referenced above.

4.4 Determination of the Sample Size

The sample size estimation is based on 2 treatment arms because the primary endpoint analyses will compare CSL346 (8 mg/kg and 16 mg/kg combined) with placebo. The planned sample size is 100 subjects with 50 subjects receiving CSL346 (8 mg/kg, n = 25 and 16 mg/kg, n = 25) and 50 subjects receiving placebo. Assuming a SD of 0.65 for the change from Baseline to Week 16 (Visit 10) in ACR following natural log transformation, a sample size of 94 subjects is estimated to provide 85% power to detect a 27% reduction in the geometric mean ACR for CSL346 versus placebo, i.e. ln (1 – 0.27) = –0.315 on the natural log scale, using a one-sided alpha = 0.10. For this study, statistical significance will be achieved with an observed treatment effect of –0.173 on the natural log scale, or approximately –16% when expressed as a percent difference in treatments, depending on the observed variability. The planned total sample size of 100 subjects accounts for an assumed 6% drop-out rate. The actual early discontinuation rate will be assessed throughout the study and up to 124 subjects may be randomized if necessary, to target 94 completed subjects (subjects who received all doses and completed the Week 16 ACR assessment).

4.5 Planned Interim Analyses and Reviews

4.5.1 Interim Analysis

For decision-making and development purposes, an interim analysis of unblinded data will be performed after enrollment is complete and all randomized subjects complete the 16-week ACR measurement (i.e., 4 weeks after the fourth dose). These results will be summarized in an interim, nonregulatory, analytical report. A formal data cutoff and unblinding will occur at this milestone. A final statistical analysis of all efficacy and safety data will occur after all subjects have completed the full 24 weeks of the study for the clinical study report.

4.5.2 Independent Data Monitoring Committee Review Meetings for Safety Monitoring

The roles and responsibilities of the Independent Data Monitoring Committee (IDMC) and the safety and efficacy date review schedules are described in the IDMC Charter. In short, the IDMC will have appropriate access to unblinded study data to facilitate periodic assessment of the efficacy and safety of the IP as well as make recommendations regarding the continuation and/or potential modification of the study. A separate IDMC Statistical Analysis Plan specifies the analyses and output for the IDMC.

5 Changes from the Protocol Planned Analyses

The following represent changes in this SAP from the protocol:

- Definition for the Per Protocol Analysis Set has been edited in this SAP and is different from the definition provided in the protocol.
- VEGF-B analyses have been removed as the assay is not available.

6 Study Analysis Sets

6.1 Screened Analysis Set

The Screened analysis set consists of all subjects who provided written informed consent.

6.2 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set comprises all subjects who were randomized. The ITT analysis set will be analyzed using the treatment to which the subject was randomized, regardless of the treatment actually received. The ITT analysis set will be used in the analysis of the primary endpoint. Any subject who receives a treatment randomization number will be considered to have been randomized.

6.3 Safety Analysis Set

The Safety Analysis Set (SAF) comprises all subjects in the ITT Analysis Set who receive at least 1 dose of CSL346 or placebo, and will be based on the actual treatment received. In the event that a subject receives both CSL346 and placebo, the subject will be included in the CSL346 group for this analysis set. Subjects receiving only placebo will be included in the placebo group.

6.4 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set is a subset of data from subjects in the ITT Analysis Set. Data is excluded for subjects violating specified entry criteria, or for data following occurrence of events which may impact ACR. Subjects with data (full or partial) to be excluded from the PP Analysis Set will be documented in the data review meeting minutes before database lock and before study data unblinding for the interim analysis. Criteria for determining the PP Analysis Set are described in Section 16.7. A second data review meeting will be held prior to final database lock.

6.5 Pharmacokinetic Analysis Set

The PK Analysis Set comprises all subjects who receive an infusion of CSL346 with at least 1 quantifiable concentration of CSL346 after administration. The actual treatment will be used for subjects in this analysis set.

6.6 Pharmacodynamic Analysis Set

The PD Analysis Set comprises subjects in the SAF for whom analysis results were obtained for at least 1 of the exploratory biomarkers of interest. The actual treatment will be used for subjects in this analysis set.

7 General Considerations

Datasets submitted to regulatory agencies will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards. Submission data will be provided in Study Data Tabulation Model (SDTM) format. Analysis data will be provided in Analysis Data Model (ADaM) format.

Statistical Analysis System (SAS) version 9.4 or higher will be used to perform all data analyses.

Continuous variables will be summarized in terms of the number of observations (n), mean, SD, median, first quartile, third quartile, minimum and maximum. Other descriptive statistics (e.g. standard error [SE], CV%) may be reported when appropriate. For repeated assessments

of continuous variables, the change from baseline will also be summarized. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics identified with the analysis in the applicable SAP section.

7.1 COVID-19 Impact

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

Protocol Deviations

Protocol deviations due to the COVID-19 pandemic will be collected in the Clinical Trial Management System (CTMS) per the study specific Protocol Deviation Plan or another method as described in the study specific protocol deviations plan.

Covance's CTMS: Pandemic related protocol deviations are identified within CTMS by using the term "COVID-19" as the first term within the deviation description. In addition, the sub-category of 'Other' will be chosen and COVID-19 will be written in the description field.

COVID-19-related protocol deviations will be summarized as sub-categories under existing categories of protocol deviations (see Section 9.2). All COVID-19 related protocol deviations will appear in the listing of protocol deviations and can be identified based on using the term "COVID-19" as the first term in the description. During the Biostatistics Data Review Meeting a review will be done to ensure that deviations are being marked accordingly.

Visit Modality, Missed Visits and Missing Assessments

Changes to subjects' visits caused by the COVID-19 pandemic will be captured for each subject in electronic data capture (EDC), on the "Visit Status" form. The EDC page is customized with the protocol specific visits and includes different options for the primary visit modality, as well as whether the missed visit/alternate visit modality is due to COVID-19. Changes to visit modality may be a protocol deviation, and this data is captured. Since assessments (e.g. vital signs, laboratory data) collected at each visit are known, the data missing due to COVID-19 can be determined.

Assessments that were missed or required alternate visit modality (e.g. televisits or home health visits) due to COVID-19 will be summarized. In addition the number of subjects with missed visits or alternate visit modality, by visit, will be summarized.

Study Treatment Discontinuation or Study Discontinuation

Subjects who have either study treatment discontinuation or study discontinuation due to

COVID-19 will have the reason captured in the electronic case report form (eCRF). On the appropriate eCRF form to record either study medication discontinuation ("End of Treatment" form) or study discontinuation ("Conclusion of Subject Participation" form), a reason will be selected which includes a field for descriptive text. The reason can be either "Withdrawal by Subject", "Physician Decision" or "Other". The associated free text field entry will include "COVID-19". When either treatment or the study is discontinued due to an AE or death, the specific corresponding AE is collected. Discontinuations due to COVID-19 adverse events (AE) will then be identified based on whether the Medical Dictionary for Regulatory Activities (MedDRA) code for the AE is included in the COVID-19 standard MedDRA query (SMQ) (Narrow).

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

Adverse Events

Adverse events associated with COVID-19, which can include a clinically significant laboratory finding like a positive test result for COVID-19, will be reported by investigators following reporting requirements as outlined in the protocol. COVID-19 associated AEs are identified via MedDRA coding. MedDRA version 24.1 has been updated to include COVID-19 specific preferred terms (PT). Relevant AEs will be identified for reporting by use of COVID-19 SMQ (Narrow). A list of those SMQs will be provided by CSL Behring. All COVID-19 associated adverse events will be included in standard AE tables as well as a COVID-19 specific AE table.

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

COVID-19 Vaccinations

For COVID-19 vaccine data collection, sites will be instructed to inquire if subject has received a COVID-19 vaccination and, if answered in the affirmative, should record each dose, exact date of administration, and manufacturer of the vaccine on the concomitant medications form. Standardized Drug Grouping (SDG) from WHO Drug Dictionary will be utilized to identify COVID-19 vaccines (see Appendix 16.6). Any vaccination related adverse events experienced by study subjects will be recorded on the AE/SAE eCRF page.

The data are planned to be summarized as follows:

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

- Listing of all subjects receiving COVID-19 vaccine.

Overall Summary of Subjects Impacted by COVID-19

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

- Subjects with any COVID-19 impact;
- Protocol Deviations;
- Missing assessment;
- Missing Visit;
- Alternate Visit Modality;
- Study Treatment Discontinuation;
- Study Discontinuation;
- Any TEAEs;
- Any Serious TEAEs;
- Receipt of COVID vaccine.

8 Data Handling Conventions

8.1 Missing Data

Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument. 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 and should be displayed as such.

Because of the design and duration of the study, missing data are inevitable. The details of handling missing data are presented in the corresponding sections of this SAP for respective analyses (e.g. primary and secondary efficacy analyses, safety analyses).

8.2 General Derived Variables

8.2.1 Reference Dates and Study Days

Reference dates are used to assign study periods relative to treatment (Section 8.4).

- The safety reference date is the treatment start date (date of IV loading dose), and will be used to calculate study day for safety measures.
- The efficacy reference date is the randomization date and will be used to calculate study day for efficacy measures.

- The PK reference date is the date and time of the IV loading dose and will be used to calculate study day/time for PK measures.

The respective study day will be calculated as (date of interest - reference date) + 1 if the date of interest occurs on or after the reference date. If the date of interest occurs before the reference date, then the study day will be calculated as (date of interest – reference date). There will be no study day zero.

8.2.2 Durations

Durations (e.g. the duration of an adverse event [AE]) are calculated in days as:

- event end date – event start date + 1, if end time or start time not available;
- event end date and time – event start date and time, if both end time and start time available.

Thus, there will be no duration of 0 if end time or start time are not available. If an AE has missing or partially missing start or end date, no duration will be calculated.

To transform durations into weeks, divide the number of days by 7; to report in months, divide the number of days by 30.4375; to report in years, divide the number of days by 365.25. These algorithms return decimal numbers, and ignore the actual numbers of days in the months or years (the calendar days) between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

8.2.3 Baseline Definition

Baseline is defined as the most recent, non-missing value before the first IP administration (including unscheduled visits) for all assessments unless otherwise stated. In case of an assessment at the same date as the first IP administration (and only the date for that assessment is available) it will be assumed the assessment was done before IP administration.

For the purposes of the analysis of albumin creatinine ratio, baseline will be defined as the geometric mean of the 6 values obtained before treatment (3 values from Visit 3 and 3 values immediately before treatment at Visit 4). If fewer than 6 values are available, the geometric mean of all the available values will be used for baseline.

Baseline for blood pressure will be the mean of the three values (or all available if fewer than three) collected immediately before the IV loading dose.

Baseline for serum creatinine will be an average of the two samples collected prior to first IP administration (Visit 3 and Visit 4). Baseline eGFR will be calculated based on the baseline

serum creatinine. These calculated baseline eGFR values will be used to define eGFR categories and covariates in statistical analyses.

For soluble tumor necrosis factor receptor 1 (sTNFR1), exploratory circulating and urinary markers, the baseline value will be an average of the two samples collected prior to first IP administration (Visit 3 and Visit 4). [Note: Exploratory circulating biomarkers are defined in Section 4.1.4 as biomarkers of lipid metabolism including but not limited to circulating total cholesterol, triglycerides, high density lipoproteins (HDL), low density lipoproteins (LDL), glycerol, non-esterified fatty acids (NEFA), and ketones. Urinary markers are defined in Section 10.3 as VEGF-A, soluble VEGF receptor 1 (VEGF-R1), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), clusterin, monocyte chemoattractant protein-1 (MCP-1) and epidermal growth factor (EGF).]

8.2.4 Change from Baseline

Change from baseline is calculated as:

- visit value – baseline value.

Percentage change from baseline is calculated as:

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

Percent change for geometric mean ACR is calculated as:

- ((geometric mean ACR at a visit / baseline geometric mean ACR) – 1) * 100%.

If either the baseline or visit value is missing, the change from baseline and percentage change from baseline is missing.

8.2.5 Multiple Assessments

All data will be reported according to the nominal visit date for which they were reported (that is, no visit windows will be applied during dataset creation and the visit will not be re-allocated if the actual visit date deviates from the planned date according to the visit schedule in the protocol). In the instance of early discontinuation from the study, data collected at discontinuation from study should be slotted to the closest scheduled visit. Unscheduled data will not be included in by-visit summaries, but will contribute to values of clinical importance and will appear chronologically in listings. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

If multiple assessments on different days are reported for the same scheduled assessment, then the latest assessment for that scheduled assessment will be analyzed unless as specified otherwise below.

8.2.6 Actual Treatment

The subjects' actual treatment will be derived from exposure data. If a subject receives a study treatment that is different from the planned treatment for the entire time of treatment, then actual treatment is the treatment actually received. In the event that a subject receives both CSL346 and placebo, the subject will be included in the CSL346 group for this analysis set. Subjects receiving only placebo will be included in the placebo group.

8.2.7 Derived Variables

Derivation of Body Mass Index (BMI)

BMI will be calculated using the following formula:

BMI (kg/m2) = Weight (kg) / [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 prior to IP administration available closest to Day 1 will be employed.

Derivation of ACR

For the purposes of the analysis of ACR, baseline will be defined as the geometric mean of the 6 values obtained before treatment (3 values from Visit 3 and 3 values immediately before treatment at Visit 4). ACR (mg/g) will be derived from first morning void (FMV) urine samples.

On-treatment assessments of ACR will be the geometric mean values from multiple FMV collections (3 FMV collections, except Visit 9 where only 2 FMV samples will be collected) at each time point.

The ACR will be provided with the lab data. Only the geometric mean values for analysis purpose will be calculated.

Derivation of eGFR

eGFR will be derived using the following the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [Levey et al. 2009]:

> eGFR = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

The standardized serum creatinine (SCr) is expressed as mg/dL. The years of age will be for all eGFR calculations the years of age collected by eCRF. “Black” will be accounted as race of “Black or African American”.

8.3 Stratification and Covariates

Stratification of subjects at enrollment will be based on whether subjects are receiving concomitant treatment with an SGLT2i. At least 50% of the subjects enrolled are to be receiving an SGLT2i. The analysis will include this stratification term in the model and results by these subgroups will be reported.

8.4 Study Periods Relative to Treatment

All data will be assigned to one of the four study time periods defined below.

Screening is defined as the time from signing of the informed consent form through Visit 2.

The **Lead-in Period** is defined as the time Post-Visit 2 (from SC saline test infusion) up to subject randomization.

The **Treatment Period** is defined as the time from randomization through Visit 9 (12 weeks after the first administration of IP).

Follow-up begins after the last administration of IP at Visit 9 through the EOS visit 12 weeks later.

9 Study Population

Unless otherwise stated, all tables and listings in Sections 9.1 – 9.4 will be based on the ITT analysis set.

9.1 Subject Disposition

The following summaries will be provided for the Screened Analysis Set by each CSL346 group (8 mg/kg or 16 mg/kg) as well as combined over CSL346 groups, placebo and total population for:

- Subjects who underwent Screening – only total;
- Screening failures with reason for failure – only total;
- Subjects eligible for randomization – only total;
- Subjects not eligible for randomization and reason for being not eligible– only total;
- Subjects randomized – by treatment and total;
- Subjects randomized but not treated – by treatment and total;
- Subjects treated – by treatment and total;

- Subjects treated who completed through the final efficacy assessment at Week 16 – by treatment and total;
- Subjects treated who discontinued from the study before the final efficacy assessment at Week 16 with reason – by treatment and total;
- Subjects treated who completed the study at Week 24 – by treatment and total;
- Subjects treated who discontinued from the study before Week 24 with reason – by treatment and total;
- Subjects entering and discontinuing each period of the study (screening, lead-in, treatment, follow-up);
- Subjects in each of the analysis sets described in Section 6.

The disposition summary will be given by study period and in addition stratified by:

- Subjects in each stratum for SGLT2i (obtained from IRT data);
- Subjects defined by level of eGFR at baseline (20-45, 45 - <60, 60 - <90, ≥90 mL/min/1.73m2);
- Subjects defined by level of ACR by 24 hr. urine at baseline (30 - ≤300, >300 - ≤1000 and >1000 mg/g).

Disposition events related to COVID-19 will also be presented by counts and percentages.

Reasons for study discontinuation will be presented in the order they are displayed in the CRF.

By-subject listing will be provided for disposition status for each subject. This will include:

- Randomization scheme based on the ITT Analysis Set;
- Subject disposition with date of screening (in case of re-screening, all screening records will be listed), date (and time) of the randomization, date (and time) of first IP administration, Week 16 date, Week 24 date, and date of completion/withdrawal;
- Screening failures with reason;
- Subjects who discontinued from the study with reason for discontinuation.

9.2 Protocol Deviations

A protocol 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 then evaluated periodically during study conduct, based on protocol deviation plan for this study developed by CSL Behring.

Deviations will be categorized as either major or minor. Major protocol deviations for subjects in the ITT Analysis Set and Per-Protocol Analysis Set will be summarized for

number and percentage of subjects with each protocol deviation, though all major and minor deviations will be listed. In addition, a summary of violations of inclusion, exclusion, and randomization criteria will be provided for ITT Analysis Set and Per-Protocol Analysis Set.

The final decision regarding protocol deviations and assignment of subjects to analysis population will be made during the blinded data review meeting.

The following by-subject listings will be provided based on the Screened Analysis Set:

- All protocol deviations (including inclusion and exclusion criteria violations, and violations of randomization criteria);
- Subject assignment to analysis sets and reasons for exclusion.

9.3 Demographic and Baseline Characteristics≥

Descriptive statistics as specified in Section 7 will be provided for continuous variables, number and percentage of subjects for categorical variables.

The following summaries will be provided for the ITT and Per-Protocol Analysis Set:

- Demographic characteristics (e.g. age, race, ethnicity, sex, baseline height, and baseline body weight, and BMI). In addition to summarization as a continuous variable, age will also be categorized and summarized by <25, 25 to ≤45, >45 to ≤65, >65 years. Country will be summarized by number and percentage of subjects in USA, Australia, New Zealand;
- Disease characteristics including the duration since diagnosis of Type II diabetes mellitus (T2DM) to enrollment in the screening period of the study, duration of albuminuria to enrollment, ACR (30 - ≤300, >300 - ≤1000 and >1000 mg/g), SGLT2i status (obtained from IRT data), eGFR status 20 - <45, 45 - <60, 60 - <90, ≥90 mL/min/1.73m^2), signs and symptoms of diabetes (e.g. diabetic retinopathy, autonomic neuropathy, peripheral diabetic neuropathy, diabetic ketoacidosis, diabetic foot ulcer, other diabetic neuropathy, other active skin ulcer), family history of diabetes (e.g. family history of type 1 diabetes, family history of type 2 diabetes)
- Medical history (coded using MedDRA – the MedDRA version will be populated in the tables output) will be presented by system organ class (SOC) and PT.

In addition, demographics will be provided stratified by SGLT2i presence, baseline eGFR and baseline ACR.

Corresponding by-subject listings will be provided. The listing for disease characteristics will include but is not limited to the year of diagnosis as well as the duration for T2DM. The

medical history listing will also provide an indicator of whether the condition was active at the time of entry into the screening period.

9.4 Prior/Concomitant Medications

Prior/concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) B3. The version will be populated in the table output.

The reported medication will be classified as 'Prior' or 'Concomitant' as follows. Note that a drug which is administered both before and after the first dose of study medication will fall into both 'Prior' and 'Concomitant' categories.

- 'Prior': if the subject has not taken any IP; or if the medication start date [/time] is before IP start date [/time]. Note that this period will include the screening and lead-in periods of the study;
- 'Concomitant' if the medication end date is after the IP start date [time]. Note this includes the treatment and follow-up periods of the study;
- If the medication start date or end date are partially or completely missing, the medication will be assigned to both 'Prior' and 'Concomitant' unless there is clear evidence that the medication stopped before IP start date (that is, the medication should be assigned only to 'Prior') or that the medication started after IP start date [/time] (that is, the medication should be assigned only to 'Concomitant').

Prior and Concomitant medications will be summarized separately showing the number and percentage of subjects taking concomitant medications by Anatomical Therapeutic Chemical (ATC) classification level 4 and PT. If the ATC level 4 coding is not available for a PT, the next available lower level ATC code will be used. Summaries of Prior and Concomitant medications will be based upon either the Safety Analysis Set or the Per Protocol Analysis Set.

Counts of the number of subjects with prior and concomitant therapies will be presented in tabular form. Counts of the number of subjects on all therapies considered standard of care will be provided separately with special note of changes in dose during concomitant treatment, refer to Appendix 16.3 for standard of care therapies. As a change in a standard of care therapy the following will be accounted:

- Any new concomitant therapy;
- Any change in dose or route or frequency of an existing therapy.

A further summary will provide treatments associated with COVID-19. Those medications will be identified by CSL Behring and a respective flag will be given in SDTM data sets, provided by CSL Behring.

The following listing will be provided:

- Prior and concomitant medication.

10 Efficacy Analyses

Data for the primary endpoint, ACR, as well as serum creatinine, eGFR, blood pressure and some biomarkers will be collected multiple times after the initiation of treatment, therefore, the primary analysis for these outcomes will be a mixed effects model repeated measures (MMRM) approach. The change from baseline to Weeks 2, 4, 8, 12, 16, and 24 will be included in the model.

Biomarkers of lipid metabolism, glycemic control and novel biomarkers of kidney function will also employ a model similar to the primary endpoint (with the exception of biomarkers measured only at the beginning and end of the study). Exploratory biomarkers will be the subject of a separate report.

10.1 Analysis of Primary Endpoint(s)

10.1.1 Primary Estimand

The primary interest is to quantify the treatment effect of CSL346 under the situation where SGLT2i may be a possible effect modifier and is included in the model. The estimand for the ITT Analysis Set is the average effect of CSL346 on the geometric mean ACR at 16 weeks averaged across subjects receiving and not receiving SGLT2i. All data collected through Week 24 will be used in the analysis.

The primary estimand in line with the primary interest of the study is described as follows:

- Treatment Condition: four SC administrations of CSL346 or placebo over a 12-week period (Day 1, Weeks 4, 8 and 12) where the primary comparison is between CSL346 at Week 16, regardless of dose, and placebo, while subjects have not died. The "treatment policy strategy" will be used, i.e. changes in dose, for example from 16 mg/kg to 8 mg/kg OR the number of subcutaneous injections, or treatment discontinuation/non-initiation, or other miscellaneous factors influencing ACR will not be taken into account in the primary analysis;
- Population: the target patient population defined by T2DM and DKD and further eligibility criteria;

- Variable: change from baseline at 16 weeks of log ACR;
- Population-level summary: difference in treatments, calculated as 100% × (geometric mean ratio of the treatment comparison – 1) based on log ACR.

10.1.2 Primary Efficacy Analysis

The primary analysis is a mixed effects model, repeated measures (MMRM) analysis of the change from baseline through 24 weeks of log ACR, with the primary treatment comparison at Week 16 (Visit 10). The model will include treatment (at 3 levels: 8 mg/kg CSL346, 16 mg/kg CSL346, and placebo), baseline log ACR, the stratification variable related to the concomitant use of SGLT2i, visit (as a categorical factor), and interactions between visit and each of the other model terms as factors. The primary comparison of interest will be calculated using a contrast of 0.5 (8 mg/kg CSL346 + 16 mg/kg CSL346) – Placebo. Please see Section 16.1 for the corresponding SAS Code for the MMRM model. Because this is an early development study and the first study in subjects with T2DM, the one-sided alpha level to be employed for this test is 0.10. Estimated treatment effect of individual CSL346 dose levels versus placebo will also be summarized. The treatment comparisons will be expressed as a percent difference in treatments, calculated as 100% × (geometric mean ratio of the treatment comparison – 1). The covariance matrix structure to be employed in the primary analysis will be an unstructured pattern. In the event of model convergence issue, a Toeplitz heterogeneous structure will be employed. If the model still fails to converge an autoregressive structure ARH(1) will be assumed.

For the purposes of this analysis, baseline will be defined as the geometric mean of the 6 values obtained before treatment (3 values from Visit 3 and 3 values immediately before treatment at Visit 4). For post-treatment, data for ACR will be collected in triplicate. The value to be employed in the analysis of each post-treatment visit will be the geometric mean of the three values. In the event of missing data, the value for a visit will be the average of the values available. There will be only one primary comparison so there is no consideration of adjustment for multiple comparisons. Comparisons of CSL346 dose levels with placebo will be considered exploratory. The primary analysis will be performed using the ITT Analysis Set. That is, the population for which we are estimating the treatment effect is according to the treatment to which subjects were randomized. To facilitate characterization of response, a line graph of ACR will be provided by relative week with the standard error of measurement (SEM) at each time point by treatment, and by treatment and baseline ACR category.

A supplemental analysis will consider the effects of COVID-19 on the primary endpoint. For subjects with treatment discontinuation due to logistical pandemic-related reasons (“Conclusion of Subject Participation” eCRF, reason of “Pandemic Related”), observations

greater than 28 days after last on-schedule SC infusion received will be excluded. For subjects who received no infusions due to logistical pandemic-related reasons, all data will be excluded. For subjects who test positive for COVID-19 infection during the study, observations on or after the diagnosis date will be excluded. If both conditions apply, then data exclusion will begin at (a) 28 days after the last SC infusion or (b) the diagnosis date, whichever is earlier.

An exploratory analysis of the primary endpoint of ACR will be a categorical analysis of the number of subjects showing a gross change in albuminuria status from baseline to Week 16. As noted above, this will compare the number of subjects in each treatment group who improve from macroalbuminuria at baseline (ACR >300 mg/g [33.9 mg/mmol]) regressing to microalbuminuria (ACR >30 and ≤300 mg/g [>3.39 and ≤33.9 mg/mmol]) or normoalbuminuria (ACR <= 30 mg/g [3.39 mg/mmol]) OR from microalbuminuria to normoalbuminuria at Week 16. For analysis of a step change in albuminuria status (i.e., from macroalbuminuria or microalbuminuria to normal albuminuria or microalbuminuria to normal albuminuria OR from microalbuminuria to macroalbuminuria) Cochran-Mantel-Haenszel test stratified for SGLT2i will be employed to compare subjects receiving CSL346 versus placebo.

10.1.3 Sensitivity Analyses of Primary Endpoint(s)

A sensitivity analysis will be conducted with regard to the primary endpoint. The analysis will be identical to the one identified above, except that the Per Protocol Analysis Set is used. In this analysis, subjects will be assigned to the treatment actually received. In the event of a decrease in dose (from 16 mg/kg to 8 mg/kg) the subject will be assigned to the highest dose treatment received. This analysis will exclude data following major protocol deviations and other factors which may influence the primary outcome. Major protocol deviations will be determined without knowledge of treatment assignment (i.e., prior to unblinding). Appendix 16.7 provides a list of major protocol deviations and other reasons for exclusion from the Per Protocol Analysis Set.

The second (to be conducted for Per Protocol Analysis Set) sensitivity analysis is a tipping point analysis that will employ multiple imputation for missing data (missing change from baseline in ACR) using multiple regression to provide multiple complete data sets [Buuren 2018]. The same MMRM model will be used to analyze the imputed complete data sets (missing ACR values will be imputed for planned ACR assessments up to the individual subjects last performed visit before EOS and EOS visit). If the original analysis indicates a significant effect, the tipping point analysis adds a value, delta, to the imputation model to assess the sensitivity of the “missing at random” assumption. In this case, the delta is

increased (decreased) until statistical significance is lost. A conclusion of the sensitivity analysis is based on whether the value of delta at the time significance is lost is interpreted as likely given the data observed.

10.1.4 Subgroup Analyses of Primary Endpoint(s)

Two a priori subgroup analyses to be considered will be based on the strata defined by the presence or absence of concomitant use of a SGLT2i and by eGFR status at baseline (20 - <45, 45 - <60, 60 - <90, ≥90 mL/min/1.73m2). Each subgroup will be analyzed in a similar manner as the primary analysis as a mixed effects model, repeated measures (MMRM) analysis of the change from baseline through 24 weeks of log ACR, with the primary treatment comparison at Week 16 (Visit 10). The model will include treatment, baseline log ACR, and interactions between visit and each of the other model terms as factors. For subgroup analysis by SGLT2i, the factor of SGLT2i is not to be included in the model. Scatterplots of ACR and/or change in ACR by eGFR will also be provided.

10.2 Analysis of Key Secondary Endpoint(s)

Blood pressure, serum creatinine and eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [Levey et al. 2009], Section 8.2.7, will employ a model similar to the primary endpoint. These endpoints will not be log-transformed prior to analysis. The analysis for these continuous endpoints is an MMRM analysis of change from baseline to each post-baseline measurement. The model will include treatment, stratification related to the concomitant use of SGLT2is, visit (as a categorical factor), and interactions between visit and each of the other model terms, as well as the corresponding baseline measurement as a covariate (refer to Section 16.1 for respective SAS code). Hypotheses testing will be identical to that of the primary endpoint. Line graphs of the mean response over time will be provided as well as by ACR status.

All of these analyses will be performed on the ITT Analysis Set.

10.2.1 Key Secondary Estimand

The treatment condition and population of the estimand for key secondary endpoints is the same as for the primary endpoint. The variable in each case will be the mean change from baseline through Week 16 in each parameter. Also, in each case, the population level summary will be the arithmetic mean change.

10.3 Analysis of Other Secondary Endpoints

Biomarkers of lipid metabolism, glycemic control and novel biomarkers of kidney function as well as weight will also employ a model similar to the primary endpoint except for the

concentration of CSL346 in urine. The analysis for continuous endpoints is an MMRM analysis of change from baseline to each post-baseline measurement (Weeks 4, 8 and 16). The model will include treatment, stratification related to the concomitant use of SGLT2i, visit (as a categorical factor), and interactions between visit and each of the other model terms, as well as the corresponding baseline measurement as a covariate (refer to Section 16.1 for respective SAS code). Treatment comparisons of interest will be similar to that of the primary endpoint. Lipid parameters will be natural log transformed prior to analysis.

Urinary biomarkers will be normalized for urine creatinine. These urinary biomarkers include urinary VEGF-A, soluble VEGF receptor 1 (VEGF-R1), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), clusterin, and monocyte chemoattractant protein-1 (MCP-1) and epidermal growth factor (EGF). Normalization is performed by dividing the urinary biomarker by urine creatinine collected at the midstream morning void taken the same day as the urinary biomarker. Normalized urinary biomarkers should be reported in units of pg/µg. To obtain these units, first convert urinary creatinine from units of mg/dL to units of µg/mL by multiplying by 10. Then divide the urinary biomarker (pg/mL) by urinary creatinine (µg/mL) to get normalized results with units of pg/µg.

A repeated measures analysis of covariance model will be employed to analyze the concentration of CSL346 in urine, collected at Day 1, Day 8, and Day 85. The repeated measures analysis of covariance model will include terms for treatment, baseline as a covariate and SGLT2i use.

All analyses for biomarker will be performed on the PD Analysis Set. Analyses for KIM-1, NGAL, EGF and MCP-1 will be performed in addition for the PP Analysis Set. Analyses for urine CSL346 concentration will be performed on the ITT Analysis Set.

10.4 Missing Data and Imputation

To avoid missing data with regard to the primary endpoint, ACR, procedures will be in place to maximize the ability to collect first morning voids for every subject at every planned visit. Likewise, every attempt will be made to retain subjects in the study once they are randomized. Therefore, it is anticipated that missing data with regard to the primary endpoint will be kept to a minimum. Imputation is only being considered for the sensitivity analysis for the primary endpoint.

10.5 Treatment Compliance

The calculation of overall compliance is based on receiving all four injections of IP. An injection of at least 80% of the planned volume will satisfy the criteria of receiving a

compliant injection at each of the 4 visits. The following summaries will be provided by treatment group:

- The number of subjects receiving all four doses of IP;
- The number of subjects receiving at least 80% of the planned infusion volume at each visit.

Compliance will be summarized for the Safety Analysis Set.

A by-subject listing will be provided including:

- By injection: the randomized and actual treatment administered, planned and actual volume of IP, individual and categorized compliance;
- Overall (across all injections): cumulative planned and cumulative actual volume of IP, individual and categorized compliance, number of injections.

Calculation of compliance and extent of exposure (as described in Section 11.1) will be based on drug accountability data collected by eCRF.

11 Safety Analyses

The safety analyses will be based on the Safety Analysis Set as defined in Section 6.3 and on the treatment which the subject received.

11.1 Extent of Exposure

Exposure to the IP will be descriptively summarized by treatment group:

- Number of subjects receiving loading dose;
- Summary statistics for Loading dose received;
- Number of subcutaneous infusions administered per visit and overall;
- Summary statistics for Total dose received [mg/kg] per visit and overall;
- Summary statistics for Total volume received (ml) per visit and overall.

Total dose received [mg/kg] will be provided with the study data. The listing of individual subject data will include all variables presented in the summary tables.

11.2 Adverse Events

AEs will be coded using the MedDRA dictionary (the MedDRA version will be populated in the tables output). AEs will start to be collected upon subject's signing of the informed consent form (ICF). AEs observed during the screening and lead-in periods of the study will be summarized separately as no treatment is received during this time. TEAEs, defined as AEs starting on or after the date of the first administration of the IP (IV loading dose),

through the end of the follow up period will be summarized. All AE tables will summarize the number and percentage of subjects with TEAEs for each of the three randomized treatment groups, for a combined column for the two CSL346 groups, as well as an overall column. All AEs regardless of whether they were treatment-emergent or not will be listed.

Where AE start dates are missing or partially missing, AEs will be assumed to be treatment-emergent, except if the partial start dates or the AE end date indicate that the AE started before the first administration of the IP (IV loading dose) during the treatment period (Section 4).

Table 2 TEAE Assignment in Case of Missing AE Start Date Elements

Missing elements of AE start	**Rule**	
Regardless of any missing information for AE start: AE end date / time < IP start date / time		non-TEAE
Otherwise (i.e., if AE end date / time ≥ IP start date / time)		
- all		TEAE
- day and month	AE start year ≥ IP start year	TEAE
	AE start year < IP start year	non-TEAE
- day	AE start month / year ≥ IP start month / year	TEAE
	AE start month / year < IP start month / year	non-TEAE
- time	AE start date ≥ IP start date	TEAE
	AE start date < IP start date	non-TEAE

If AE start dates or end dates are missing or partially missing for an AE, no duration will be calculated. If for a TEAE the relationship to study treatment is missing the worst case will be assumed for summarizing analysis (i.e. the relationship to study treatment will be assumed to be "Related"). A missing severity for a TEAE will be assumed for summaries as "Severe". For non-TEAEs no imputation will be done in case of missing study treatment relationship or severity. No other imputations for missing AE information will be done.

The AESIs for this study are defined as:

- Injection site reactions (PTs as identified through a standard MedDRA query, provided by CSL Behring);
- Increase in serum creatinine, defined as a confirmed increase in serum creatinine from baseline of ≥0.3 mg/dL;

- Albuminuria, defined as a confirmed increase in urinary ACR of > 2-fold increase (doubling) from baseline with additional evidence suggesting Acute Kidney Injury (AKI);
- Increased blood pressure, defined as an observed SBP ≥180 mmHg and/or DBP ≥120 mmHg or an increase from Baseline in either SBP or DBP ≥20 mmHg and greater than 160/105 mmHg;
- A cardiac event will be defined as any clinically-meaningful change from Baseline in cardiac-related parameters, such as electrocardiogram (ECG) intervals, cardiac troponin levels [Thygesen et al, 2018], or left ventricular ejection fraction (LVEF), as reported in the cardiac AESI-specific eCRF.

For tabulated summaries injection site reactions, increase in serum creatinine, albuminuria, and increased blood pressure and cardiac events will be identified in the eCRF as marked by the investigator.

An overview summary of TEAEs, including number and percentages of subjects as well as the number of events, will be provided including the following:

- Any TEAE;
- TEAEs related to study treatment;
- TEAEs leading to discontinuation of study treatment (obtained from AE eCRF);
- TEAEs leading to study withdrawal (obtained from “End of Treatment” or “Conclusion of Subject Participation” eCRF);
- TEAEs leading to dose interruptions;
- TEAEs by maximum severity (without number of events or TEAE rate);
- Treatment-emergent AESIs;
- Serious TEAEs;
- Serious TEAEs related to study treatment;
- Fatal TEAEs.

The above overall AE table will also be provided for the whole study, for the Treatment Period and for the Follow-up Period, and for Follow-up Period separately. In addition, the overview table will be stratified by SGLT2i as well as ACR and eGFR status separately at baseline.

The following frequency tables will be generated for TEAEs, including number and percentages of subjects and the number of events:

- TEAEs by SOC and PT;
- TEAEs by PT;

- TEAEs by PT through Week 16;
- TEAEs by PT from Week 16 through Week 24;
- TEAEs by PT, stratified by SGLT2i;
- TEAEs by PT, stratified by baseline eGFR (<60 and eGFR>=60 mL/min/1.73m2);
- TEAEs by SOC, PT, and maximum severity (without number of events);
- Related TEAEs by SOC and PT;
- Related TEAEs by PT;
- Treatment-emergent AESIs by PT;
- Serious TEAEs by SOC and PT;
- Related serious TEAEs by SOC and PT;
- TEAEs with result in drug discontinuation;
- TEAEs related to COVID-19 infection.

AEs will be presented in summaries by decreasing overall frequency (overall frequency as the number of subjects with that AE). In case of two AEs having the same overall frequency, the AEs will be ordered alphabetically.

The following by-subject listings will be provided:

- All AEs;
- SAEs;
- AEs leading to study withdrawal or permanent discontinuation of study treatment;
- AESIs by type of AESI.

11.3 Clinical Laboratory Evaluations

The following hematology and serum biochemistry laboratory tests will be summarized by visit and by the three randomized treatment groups, including a combined column for the two CSL346 groups. The summaries will be provided for the analysis population as described in Section 11. Data for urinalysis will only be listed.

Hematology: Hemoglobin, hematocrit, erythrocytes (RBC) count (RBC indices of MCV; MCH; MCHC; RDW, if available), total and differential leukocyte (WBC) counts (neutrophils; neutrophil band forms, lymphocytes; monocytes; eosinophils; basophils), reticulocytes, and platelet count.

Serum Biochemistry: Albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total), bilirubin (direct), blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, creatinine, creatinine kinase, C reactive protein (CRP), glucose, potassium, sodium, protein (total), cholesterol (total), HDL cholesterol, LDL

cholesterol, bicarbonate, Lactatdehydrogenase (LDH), gamma-glutamyl-transferase (GGT), triglycerides, urate (uric acid), international normalized ratio (INR), prothrombin time, and activated partial thromboplastin time (aPTT).

Urinalysis: Bilirubin, glucose, nitrites, pH, leukocyte esterase, blood, ketones, urobilinogen, protein, and specific gravity.

Standard safety laboratory data from the central lab will be presented in SI units (except as presented in Appendix 16.10 and in the order presented as given above. Measured laboratory values will be summarized descriptively by scheduled visit. Changes from baseline for laboratory parameter will be derived and presented in the same way as measured laboratory values.

Samples for standard urinalysis will be taken at screening and Day 1.

A laboratory value that is outside the reference range is either high abnormal (value above the upper limit of the normal [ULN] reference range) or low abnormal (value below the lower limit of the normal [LLN] reference range). An abnormal laboratory value is not necessarily of potential clinical interest. For each of the hematology and chemistry lab tests, shift tables will be constructed to compare the individual subject baseline value with respect to the normal range to their Week 24 (or last observed value for dropouts before Week 24) value with respect to the normal range.

The incidence of potentially clinically significant abnormal values for selected laboratory measurements will be summarized by visit during the Treatment Period and Follow-up Period. Table 3 gives the ranges of potential clinical concern for selected laboratory measurements.

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

Mean plots +/- SD over time will be provided for lab parameter of hematology and serum biochemistry. Hy's law plots for AST versus bilirubin (total) and ALT versus bilirubin (total) will be provided.

Table 3 Laboratory Values of Potential Clinical Importance

Laboratory Parameter	Potential Clinical Importance Range	Unit
ACR (Urine)	Change from baseline ≥1.5	mg/g
Platelet Count	<40 or >999	10^3/UL
Hematocrit	<20 or >60	%
Hemoglobin	<7 or >20	g/dL
White Blood Cell Count (WBC)	<3 or >20	10^9/L
Neutrophil Count	<1.5	10^9/L
Serum Creatinine	Change from baseline (>0.3 and <0.7) OR Change from baseline ≥0.7	mg/dL
Fasting Glucose	<70 or ≥250	mg/dL
Nonfasting Glucose	<40 or >450	mg/dL
Potassium	<3 or ≥5.5	mEq/L
Troponin-I	>ULN	ng/mL
Alkaline phosphatase	>2 x ULN	U/L
Total bilirubin	>2 x ULN	µmol/L
ALT/SGPT	>3 x ULN	U/L
AST/SGOT	>3 x ULN	U/L

A by-subject listing of all laboratory values including flag for values out of normal range and clinically importance will be provided. Listings will include in general all visits (scheduled and unscheduled).

11.4 Other Safety Measures

11.4.1 Immunogenicity

The number and percentage of subjects with a positive immunogenicity test (presence of binding antibodies to CSL346) at any time (Weeks 4, 8, and 16) during treatment and follow-up period will be summarized by treatment group, including a combined CSL346 treatment group. A treatment comparison of combined CSL346 treatment group vs. placebo treatment group will be done by using Fisher's Exact Test.

A by-subject listing for immunogenicity will be provided.

11.4.2 Vital Signs

The vital signs will be summarized by visit and by the three randomized treatment groups and a combined CSL346 treatment group. The summaries will be provided for the analysis population as described in Section 11.

The following summaries will be provided for systolic and diastolic blood pressure, heart rate, body temperature and body weight:

- Values of vital signs by scheduled visit,
- Change from baseline by scheduled visit.

Vital signs will be assessed as a triplicate measurement. For purpose of analysis the mean value of such triplicate parameter assessments will be used.

Vital sign values of potential clinical importance will be determined by using the criteria detailed in Table 4. The number and percentage of subjects with vital signs of potential clinical importance will be summarized by visit and at any time for the three randomized treatment groups and a combined CSL346 treatment group.

A by-subject listing of all vital sign data (scheduled and unscheduled visits) will also be presented. The listing will include a flag for values of potential clinical importance.

Table 4 Vital Signs of Potential Clinical Importance

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Hypertensive AESI – Flag for crisis (definitions are the same; clinical presentation defines a crisis)	SBP ≥180 mmHg and/or DBP ≥120 mmHg OR an increase from Baseline in either SBP or DBP ≥20 mmHg and SBP/DBP greater than 160/105 mmHg	mmHg
DBP	<45	mmHg
SBP	<85	mmHg
Heart rate	<40 or >110	bpm

11.4.3 ECG

The ECG parameter (PR interval, QRS duration, QT interval, QTcF, QTcB, heart rate) and their changes from baseline will be summarized by visit and by the three randomized treatment groups and a combined CSL346 treatment group. The summaries will be provided for the analysis population as described in Section 11.

ECG assessments will be done as a triplicate measurement. For purpose of analysis the mean value of such triplicate parameter assessments will be used.

For QTcF, PR interval, QRS interval and heart rate, values of potential clinical importance will be determined by using the criteria detailed in Table 5. The number and percentage of subjects with those values of potential clinical importance will be summarized by visit and at any time for the three randomized treatment groups and a combined CSL346 treatment group. Subgroup summaries will also be provided by gender. The overall interpretation of ECG will be summarized at the same time points and treatment groups.

Table 5 ECG Parameters of Potential Clinical Importance

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
QTcF Interval	>450 OR <500 or ≥500 OR ≥500 OR increase from Baseline ≥60 or increase from Baseline between >30 and <60	msec
Absolute PR Interval	<120 or >210	msec
Absolute QRS Interval	<75 or >110 or >120	msec
Heart rate	<50 or ≥120	bpm

A by-subject listing of all ECG data (scheduled and unscheduled visits) will also be presented. The listing will include a flag for values of potential clinical importance.

12 Pharmacokinetic Analyses

The PK analysis will be performed using the PK Analysis Set.

All non-compartmental analyses are to be performed according to CSL SOP PK-GDL-01 and will be performed by CSL Behring Clinical Pharmacology & Pharmacometrics by using WinNonlin® version 8.1 or later. Alternatively CSL Behring may contracting a Clinical Research Organisation to derive the PK parameter.

After data base lock, CSL Behring Clinical Pharmacology & Pharmacometrics will produce all SDTM domains needed for the PK analysis (serum PK analysis). The PC domain containing the CSL346 concentrations, nominal blood sampling times, actual sampling time relative to the start of the dosing, and actual dosing and the PP domain containing the PK parameters will be provided. Any CSL346 serum concentrations which will have been excluded from the derivation of the PK parameters will be flagged in the data.

Parexel will produce the TFLs for the CSL346 serum concentrations and the PK parameters as specified below.

Population PK analyses will be performed according to the Modeling and Simulation Analysis Plan and reported separately.

12.1 Drug Concentration Measures

The handling and imputation of below limit of quantification (BLQ) values for PK parameter derivation is described in (1), (2), (3), and (4). The imputation rules below will be used for summary statistics of CSL346 serum concentrations. The summaries will be given by planned time point.

- The sampling time of pre-dose samples relative to start of the dose infusion will be treated as zero;
- Concentration values below BLQ in pre-dose samples and in samples taken before the time of the first quantifiable concentration will be treated as zero;
- Post-dose BLQ concentrations flanked by quantifiable concentrations will be set to missing;
- Post-dose BLQ concentrations after the last quantifiable point will be set to missing for summary statistics of serum concentrations;
- The mean/median value at a time point where one or more samples have BLQ values will be reported (in tabular or graphical fashion) even if the mean/median value is BLQ of the assay;
- Zero mean or median values will be included in summary tables.

The lower limit of quantification for CSL346 in serum is 80 ng/mL and in urine it is 80 ng/mL. Concentrations that are below BLQ should be reported as "< LLOQ" in listings.

It should be noted that a high proportion of BLQ values may affect the summary statistics; if more than 50% of the values are imputed (i.e. BLQ), then the summary statistics (mean, SD, median, quartiles) will not be displayed.

Summary statistics for concentration-time data will include the percentage of BLQ values relative to the total N

> %BLQ = 100 * (number of subjects who have BLQ values / total number of subjects) at each time point.

Descriptive statistics will be provided as outlined in Section 7, and in addition the CV% (CV% = 100* standard deviation / mean) and geometric mean.

Individual CSL346 serum concentration plots will be plotted versus actual sampling time from predose on Day 1 through predose on Day 29. Each plot will have a graph on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. log-linear plot).

Plots for mean (± SD) CSL346 serum concentrations (on linear and on log-linear scales) versus nominal (planned) time will be provided from predose on Day 1 through predose on Day 29. All treatment groups will be overlayed for the mean plot. If more than 50% of the individual values are BLQ, the mean and SD will be set to missing in the plots.

Additionally, a box and whisker plot on nominal sampling time for serum concentrations at predose time points on Days 29, 57, 85, as well as concentrations on Days113 and 169 will be provided. All treatment groups will be displayed in one plot.

Serum concentrations excluded from the derivation of the PK parameters will also be excluded from the summary statistics and the mean plots. A footnote will indicate if serum concentrations have been excluded from the analysis.

A by-subject listing of CSL346 serum concentrations with the concentrations flagged that have been excluded from the derivation of the PK parameters based on the PK Analysis Set will support the summaries.

Urine concentration of CSL346 will be summarized by nominal time point using the same summary statistics as for serum concentration and a by-subject listing will be provided.

12.2 Deriving and Summarizing Pharmacokinetic Parameters

For subjects belonging to the PK Analysis Set, the PK parameters provided in Appendix 16.2 will be determined from the CSL346 serum concentration-time data.

The PK parameter derivation including imputation of the values BLQ and missing data will be conducted in accordance to (1), (2), (3), and (4) which gives guidance on how to derive PK parameters in the presence of missing data.

PK parameters of CSL346 will be summarized with the following statistics being provided.

Variable	**Statistical Parameters:**
C_{max} after IV loading dose, C_{max} after first SC dose, C_{trough} after each SC dose, AUC_{day1}, $AUC_{0\text{-}28d}$, CL after first SC dose	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
T_{max} after IV loading dose, T_{max} after first SC dose,	n, minimum, median, and maximum

The geometric CV% will be calculated as 100* square root of ((anti-log of variance for log transformed data) minus 1)) CV%=100*sqrt(exp(ln(SD^2))-1).

All PK parameters will be reported to at least 3 significant digits, but to no more significant digits than the precision of the original serum concentration data.

A by-subject listing of CSL346 PK parameters based on the PK Analysis Set will be provided.

12.3 Pharmacokinetic Statistical Analyses

Dose-adjusted PK parameters of AUC_{day1}, $AUC_{0\text{-}28d}$, C_{max} after IV loading dose, and C_{max} after first SC dose will be natural log transformed and analyzed in an analysis of variance model, comparing the 8 mg/kg and 16 mg/kg dose levels. The model will be based on the dose level as the only effect. The estimate and 90% CI for the difference of 16 mg/kg – 8 mg/kg will be exponentiated to obtain the point estimate and CI for the geometric mean ratio. Dose proportionality is supported when the 90% CI includes the 1.

Graphical displays of CSL346 will include a separate display for each natural log transformed PK parameter versus natural log transformed dose to evaluate dose proportionality.

13 Pharmacodynamic and Biomarkers Analyses

Unless otherwise specified, these analyses will be based on the PD Analysis Set.

13.1 Biomarker Analyses

Analysis of biomarker is included in efficacy analysis, please refer to Section 10.3.

14 Pharmacokinetic/Pharmacodynamic Analyses

A correlation plot $AUC_{0\text{-}28d}$ versus baseline ACR will be provided. The Spearman correlation coefficient, a regression line, and slope and intercept of regression will be added to the plot. The same plot will be provided for CL versus baseline ACR and for $AUC_{0\text{-}28d}$ versus baseline eGFR and for CL versus baseline eGFR.

A correlation plot of C_{trough} on Day 29 versus change from baseline in ACR at Day 29 will be provided. The Spearman correlation coefficient, a regression line, and slope and intercept of regression will be added to the plot. The same plot will be provided for the assessment at Days 57, 85, and 113. A similar plot will be provided for CL versus change from baseline in eGFR on Day 29.

A correlation plot of urine CSL346 concentration on Day 8 versus baseline ACR on Day 8 will be provided. The Spearman correlation coefficient, a regression line, and slope and intercept of regression will be added to the plot. The same plot will be provided for urine CSL346

concentration at Day 85 versus ACR at Day 85. A correlation plot of urine CSL346 concentration at Day 85 versus change from baseline in ACR at Day 85 will also be provided. The same series of plots will be provided for urine CSL346 concentration versus baseline eGFR and urine CSL346 concentration versus the change in eGFR.

The correlation of systolic blood pressure, measured at 60min after SC dosing at Visit 4, versus AUC_{day1}, starting after IV administration, will be presented. The Spearman correlation coefficient, a regression line, and slope and intercept of regression will be added to the plot. The same plot will be provided for diastolic blood pressure.

A correlation plot of systolic blood pressure versus C_{trough} at Day 29 will be provided. The Spearman correlation coefficient, a regression line, and slope and intercept of regression will be added to the plot. The same plot will be provided for the assessments at Days 57, 85, and 113. A similar series of plots will be provided for diastolic blood pressure versus C_{trough} at Days 29, 57, 85, and 113.

A correlation plot of change from baseline in total cholesterol versus C_{trough} at Day 29 will be provided. The Spearman correlation coefficient, a regression line, and slope and intercept of regression will be added to the plot. The same plot will be provided for assessments at Days 57, 85, and 113. The same series of plots will be provided for all other biomarkers.

A population PKPD analysis may be used to further assess characterization of PK versus PD endpoints. If such an analysis will be done, this work will have a separate analysis plan and report.

15 References

(1) Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction. J Am Coll Cardiol. 2018 Oct 30;72(18):2231-2264.

(2) Andrew S. Levey, MD, Lesley A. Stevens, MD, MS, FRCP(C), Christopher H. Schmid, PhD, Yaping (Lucy) Zhang, MS, Alejandro F. Castro, III, MPH, Harold I. Feldman, MD, MSCE, John W. Kusek, PhD, Paul Eggers, PhD, Frederick Van Lente, PhD, Tom Greene, PhD, and Josef Coresh, MD, PhD, MHS, for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), A New Equation to Estimate Glomerular Filtration Rate, Ann Intern Med. 2009 May 5; 150(9): 604–612.

(3) van Buuren S, Chapman & Hall, Flexible Imputation of Missing Data, 2 ed., Hoboken (2018)

(4) PK-GDL-01, Guideline on the Conduct of Non-compartmental Pharmacokinetic Analyses, CSL Behring.

16 Appendices

16.1 SAS Code

SAS code for MMRM analysis

```
Ods graphics on;
Proc mixed data=data_set method=reml plots=residualpanel;
  Class treatment visit patient sglti_yn;
  Model chglnacr =treatment visit baseline sglti_yn
treatment*visit sglti_yn*visit baseline*visit / alpha=0.20 cl
ddfm=kr covb solution;
  Repeated visit / type=un subject=patient r rcorr;

* *** Estimate for treatment difference at 2 weeks *** *;
  Estimate "CSL08 vs. PBO at 2 weeks" treatment 1 0 -1
treatment*visit 1 0 0 0 0 0    0 0 0 0 0 0    -1 0 0 0 0 0 / CL
alpha=0.2;
  ESTIMATE "CSL16 vs. PBO at 2 weeks" treatment 0 1 -1
treatment*visit 0 0 0 0 0 0    1 0 0 0 0 0   -1 0 0 0 0 0 / CL
alpha=0.2;
  ESTIMATE "CSL vs. PBO at 2 weeks" treatment 0.5 0.5 -1
treatment*visit 0.5 0 0 0 0 0    0.5 0 0 0 0 0    -1 0 0 0 0 0 / CL
alpha=0.2;

* *** Estimate for treatment difference at 16 weeks *** *;
  Estimate "CSL08 vs. PBO at 16 weeks" treatment 1 0 -1
treatment*visit 0 0 0 0 1 0    0 0 0 0 0 0    0 0 0 0 -1 0 / CL
alpha=0.2;
  ESTIMATE "CSL16 vs. PBO at 16 weeks" treatment 0 1 -1
treatment*visit 0 0 0 0 0 0    0 0 0 0 1 0   0 0 0 0 -1 0 / CL
alpha=0.2;
  ESTIMATE "CSL vs. PBO at 16 weeks" treatment 0.5 0.5 -1
treatment*visit 0 0 0 0 0.5 0    0 0 0 0 0.5 0    0 0 0 0 -1 0 / CL
alpha=0.2;

  Lsmeans treatment treatment*visit / diff cl;
run;
Ods graphics off;
```

Where:

- chglnacr is the repeated measure of change in log ACR collected at Weeks 2, 4, 8, 12, 16 and 24;
- treatment takes on three levels (CSL346 8 mg/kg, CSL346 16 mg/kg and placebo)

- sglt2i_yn is the stratification variable associated with the presence or absence of a concomitant SGLT2i at entry into the trial;
- baseline is the baseline log ACR used as a covariate in the model;
- visit is the time variable;

SAS code for multiple imputation

```
Proc mi data=data_set out=data_set_imputed nimpute=10
seed=xxxx round=0.01;
   Var treatment visit sglti_yn patient chglnacr;
   Monotone reg(chglnacr = treatment visit sglti_yn patient);
run;
```

Where:

- chglnacr is the repeated measure of change in log ACR collected at Weeks 2, 4, 8, 12, 16 and 24;
- treatment takes on three levels (CSL346 8 mg/kg, CSL346 16 mg/kg and placebo)
- sglt2i_yn is the stratification variable associated with the presence or absence of a concomitant SGLT2i at entry into the trial;
- visit is the time variable;

16.2 PK Parameters

Term	Definition [unit]	Calculation method
AUC_{day1}	Partial AUC from time point 0 to time point 1 day [mass * time *volume^{-1}]	AUC from the time of dosing to subject released from the clinic on Day 1, using the linear up/log down trapezoidal rule
AUC_{0-28d}	Partial AUC from time point 0 to 28 days [mass * time *volume^{-1}]	AUC from the time of dosing to a specified 28 days, using the linear up/log down trapezoidal rule
C_{max}	The maximum observed in serum [mass * volume^{-1}]	
C_{trough}	Observed concentration at the end of a dosing interval, immediately before the next dose administration [mass * volume^{-1}]	
CL	The total body clearance of drug after IV dose or extravascular dose with known bioavailability [volume * time^{-1}]	When the extrapolated area contributes more than 30% to the total $AUC_{0-\infty}$, data will be excluded from summary statistics unless justification is provided to support the validity of $AUC_{0-\infty}$.
T_{max}	The time to reach maximum (peak) drug concentration in measured biological fluid [time]	

16.3 Standard of Care Therapies

Drug Class	ATC Code (ATC 2)
Antihypertensive drugs	C02
Diuretic drugs	C03
Peripheral vasodilators	C04
Beta blocking agents	C07
Calcium channel blockers	C08
Agents acting on the renin-angiotensin system	C09

16.4 Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

Drug Class	ATC Code (ATC 4)
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	A10BK

16.5 SMQs for COVID-19 associated AEs

SMQ	Code	Level
Asymptomatic COVID-19	10084459	PT
Coronavirus infection	10051905	PT
Coronavirus test positive	10070255	PT
COVID-19	10084268	PT
COVID-19 immunisation	10084457	PT

SMQ	Code	Level
COVID-19 pneumonia	10084380	PT
COVID-19 prophylaxis	10084458	PT
COVID-19 treatment	10084460	PT
Exposure to SARS-CoV-2	10084456	PT
Multisystem inflammatory syndrome in children	10084767	PT
Occupational exposure to SARS-CoV-2	10084394	PT
SARS-CoV-2 antibody test positive	10084491	PT
SARS-CoV-2 carrier	10084461	PT
SARS-CoV-2 sepsis	10084639	PT
SARS-CoV-2 test false negative	10084480	PT
SARS-CoV-2 test positive	10084271	PT
SARS-CoV-2 viraemia	10084640	PT
Suspected COVID-19	10084451	PT

16.6 COVID-19 Vaccines

Drug Class	ATC Code
COVID-19 vaccines	J07BX03

16.7 Factors to be Addressed in Per Protocol Analysis Set

The following define major events which could result in subjects' data being removed from the per protocol analysis set. Subjects' data may be removed completely or from the time of the major event up to the end of subject's study participation.

At a specific time point, ACR measurements are to be used in summaries and analysis as long as there are at least 2 FMVs for that time point (4 FMVs for baseline) available.

- Extrinsic factors with the potential to impact ACR during treatment period. For any such occurrences, data points at or beyond the date of the occurrence will be excluded from analysis. [These data will be provided by CSL.]
  - Protocol deviations:
    - Subjects with substantial change in blood pressure medications or DKD medications;
    - Prohibited concomitant medications;
    - Initiation of lipid lowering agent;
    - Change in SGLT2i doses;
    - Change in dose in agents that impact tubular secretion of serum creatinine (fibrates).
    - Missed intermittent dose
  - Cardiac AESI with heart failure.

- Study drug [to be derived by Parexel]:
  - For subjects receiving fewer than 4 doses of the investigational product, all data on or after the date of the last dose + 4 weeks + 1 day will be excluded. If no dose is administered then all data for that subject will be excluded.

- Violation of study entry criteria. In these cases, all data from these subjects will be excluded from analysis. [These data will be provided by CSL.]
  - Baseline Glycosylated HbA1c >=12 %;
  - Change in SCr from Visit 1 (<63 Days before Day 1) to Visit 2 (Day -21) > 0.3 mg/dL (26.5 µmol/L);
  - Uncontrolled hypertension: SBP > 160 mmHg or DBP > 100 mmHg prestudy (SBP>150 mmHg at randomization).

16.8 Schedule of Assessments

Study Period	Screening		Lead-in	Treatment						Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	EOS
Week	Up to –6 weeks		–1	NA	1	2	4	8	12	16	24
Study Day	≤ 63 days[A] before Day 1	–21	–7	1	8	15	29	57	85	113	169
Visit Window (Days)	NA	± 7	± 4	NA	± 3	± 3	± 3	± 5	± 5	± 7	± 7
Informed consent / IRT registration	X										
Eligibility criteria	X	X									
Randomization criteria[B]			X	X							
Medical history	X										
Demographics	X										
Virology testing	X										
Pregnancy test (FCBP)[C]	X		X	X			X	X	X	X	X
Physical examination[D]		X	X	X	X	X	X	X	X	X	X
Vital signs[E]	X	X	X	X	X	X	X	X	X	X	X
Height and weight[F]	X		X	X	X	X	X	X	X	X	X
12-lead electrocardiogram[G]	X		X	X	X	X	X	X	X	X	X
Echocardiogram[H]	X										
Troponin-I and BNP	X		X	X	X	X	X	X	X	X	X
Coagulation (PT / INR and aPTT)	X										
HbA1c	X			X						X	X
Hematology and biochemistry	X	X[I]	X	X	X	X	X	X	X	X	X
Urinalysis	X			X							
Timed 24-hour urine[J]	X				X				X		
First morning void urine[K]			x3	x3		x3	x3	x3	x2	x3	x3
Morning midstream urine[L]			X	X			X	X		X	

Study Period	**Screening**		**Lead-in**	**Treatment**						**Follow-up**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**EOS**
Week	**Up to –6 weeks**		**–1**	**NA**	**1**	**2**	**4**	**8**	**12**	**16**	**24**
Study Day	**≤ 63 days[A] before Day 1**	**–21**	**–7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**169**
Visit Window (Days)	**NA**	**± 7**	**± 4**	**NA**	**± 3**	**± 3**	**± 3**	**± 5**	**± 5**	**± 7**	**± 7**
SC normal saline test infusion		X									
Randomization				X							
IRT IP assignment				X			X	X	X		
IP administration[M]				IV and SC			SC	SC	SC		
Serum PK sampling[N]				X	X	X	X	X	X	X	X
Local tolerability assessment				X	X	X	X	X	X	X	
Adverse events	From ICF Signature through Last Visit										
Concomitant medications	From ICF Signature through Last Visit										
Immunogenicity				X			X	X		X	
Biomarker sample (blood)[O]			X	X			X	X		X	

ACR = albumin-to-creatinine ratio; aPTT = activated partial thromboplastin time; BNP = b-type natriuretic peptide; BP = blood pressure; EOS = End of Study; FCBP = female subjects of childbearing potential; HbA1c = hemoglobin A1c; ICF = informed consent form; IMP = investigational medicinal product; INR = international normalized ratio; PT = prothrombin time; IP = investigational product; IRT = interactive response technology; IV = intravenous(ly); PK = pharmacokinetic; SC = subcutaneous(ly); VEGF = vascular endothelial growth factor.

Notes to the Schedule of Assessments:

A: Screening Visit 1 should be performed within 6 weeks before Screening Visit 2.

B: Randomization criteria will include evaluations of BP, serum creatinine, and troponin.

C: A serum pregnancy test will be performed at Screening for FCBP; serum or urine pregnancy tests will be performed at all other indicated visits.

D: A comprehensive physical examination will be performed at Visit 2 (Day –21) and at EOS. An abbreviated physical examination will be performed for all other indicated visits.

E: Vital signs include BP (systolic and diastolic), temperature, and pulse. Blood pressure measurements should be taken in triplicate before all other assessments. Vital signs in general will be collected before any blood samples that are collected at the same time point. At Visit 2 (Day –21), BP will be the only vital sign collected. Instructions for measuring BP will be provided in the Manual of Operations. At Visit 4 (Day 1), vital sign measurements will be taken predose, at 30, 60, and 120 minutes (± 15 minutes) after the first IV dose of IP (before the first SC dose of IP) is administered, then at 30 and 60 minutes (± 15 minutes) after SC dosing.

F: Height will be measured at Screening only.

G: Electrocardiograms must be performed in triplicate before any blood samples that are collected at the same time point.

H: A local assessment of echocardiogram will be performed during Screening unless an echocardiogram was performed for non-study-related reasons within 3 months before Screening.

I: At Visit 2 (Day –21), a blood sample will be collected for determination of serum creatinine only.

J: A timed 24-hour urine sample will be collected to assess eligibility (ACR) at Screening (Baseline), and to measure CSL346 levels in urine at subsequent indicated visits.

K: Subjects will collect urine from their first morning void on 3 consecutive days (2 consecutive days for Visit 9) leading up to and including the morning of each indicated visit.

L: Morning midstream urine samples will be collected to evaluate exploratory biomarkers and will also be stored for future research analyses.

M: Specific instructions for administration of IP are provided in the IMP Handling Manual. At Visit 4 (Day 1), an initial loading dose of IP will be administered by IV, followed at least 2 hours (but no more than 6 hours) later by the subject's normal prescribed dose by SC infusion. Subsequent doses of IP will be administered by SC infusion.

N: Serial blood samples for PK will be collected at Visit 4 (Day 1) predose, at 30 (± 5 minutes), 60 (± 10 minutes), and 120 (± 10 minutes) minutes after the first IV dose of IP (before the first SC dose of IP) is administered, then after the final vital signs measurement. Single PK samples will also be collected at all subsequent visits (before treatment on SC dosing days).

On biomarker blood sample collection days, subjects will arrive following a minimum 6-hour fast. Blood biomarker samples will be collected to evaluate pharmacodynamic and exploratory biomarkers and will also be stored for future research analyses.

16.9 Directionality of One-sided Tests

Since treatment comparisons in this study are based on one-sided tests, we need to designate the direction of these tests. Directionality and method for calculating one-sided p-value from the two-sided p-value is specified in the table below.

Parameter Name	Better (Lower or Higher)	Comment	One sided p-value calculated as:
Biomarkers of Lipid Metabolism:Total Cholesterol	Lower	Compared to PBO	estimate < 1 p-one sided=p/2 estimate >= 1 p-one sided=1-p/2
Biomarkers of Lipid Metabolism: Triglycerides –	Lower	Decreased triglycerides in the fed state, compared to PBO could indicate activity, but in fasted samples, no change would be predicted.	estimate < 1 p-one sided=p/2 estimate >= 1 p-one sided=1-p/2
Biomarkers of Lipid Metabolism: HDL –	Higher	Compared to PBO	estimate < 1 p-one sided=1-p/2 estimate >= 1 p-one sided=p/2
Biomarkers of Lipid Metabolism: LDL –	Lower	Compared to PBO	estimate < 1 p-one sided=p/2 estimate >= 1 p-one sided=1-p/2
Biomarkers of Lipid Metabolism: (Fasting) Glycerol –	Higher	Smaller (or no) increase in fasting glycerol, NEFA, ketones compared to PBO could indicate activity	estimate < 1 p-one sided=1-p/2 estimate >= 1 p-one sided=p/2
Biomarkers of Lipid Metabolism: (Fasting) NEFA –	Higher		estimate < 1 p-one sided=1-p/2 estimate >= 1 p-one sided=p/2
Biomarkers of Lipid Metabolism: (Fasting) Ketones –	Higher		estimate < 1 p-one sided=1-p/2 estimate >= 1 p-one sided=p/2
Biomarkers of VEGF Family: Urinary VEGF-A	Lower	Decrease in total VEGF-A compared to PBO could indicate activity	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
Biomarkers of VEGF Family: Urinary Soluble VEGF-R1	Lower	Decrease in total VEGF-R1 compared to PBO could indicate activity	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
Biomarkers of Tubular Injury: KIM-1	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2

Biomarkers of Tubular Injury: NGAL	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
Biomarkers of Tubular Injury: MCP-1	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
Biomarkers of Tubular Injury - EGF	Higher	Compared to PBO	estimate < 0 p-one sided=1-p/2 estimate >= 0 p-one sided=p/2
Biomarkers of Tubular Injury: Clusterin	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
Circulating Biomarker of Inflammation: sTNFR1	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
ACR	Lower	Compared to PBO	estimate < 1 p-one sided=p/2 estimate >= 1 p-one sided=1-p/2
eGFR	Higher	Compared to PBO	estimate < 0 p-one sided=1-p/2 estimate >= 0 p-one sided=p/2
Serum Creatinine	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
Blood pressure	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
Weight	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
HbA1C	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2
Fasting glucose	Lower	Compared to PBO	estimate < 0 p-one sided=p/2 estimate >= 0 p-one sided=1-p/2

16.10 Non-SI Units

Certain parameters should be reported in non-SI units (conventional units). These parameters, along with the specified units for reporting, are shown in the table below.

Parameter	**Conventional Units**	**SI Units**	**Conversion Factor**
Albumin-creatinine ratio	mg/g	mg/mmol	To convert ACR in mg/mmol to mg/g, divide by 0.113
Creatinine	mg/dL	µmol/L	To convert Creatinine in µmol/L to mg/dL, divide by 88.4
HbA1c	%	HbFract	To convert HbA1c in HbFract to %, multiply by 100
Total cholesterol	mg/dL	mmol/L	To convert Total cholesterol in mmol/L to mg/dL, divide by 0.0259
HDL cholesterol	mg/dL	mmol/L	To convert HDL cholesterol in mmol/L to mg/dL, divide by 0.0259
LDL cholesterol	mg/dL	mmol/L	To convert LDL cholesterol in mmol/L to mg/dL, divide by 0.0259
Triglycerides	mg/dL	mmol/L	To convert Triglycerides in mmol/L to mg/dL, divide by 0.0113

Signature Page

CSL346_2001 - Statistical Analysis Plan - v3 - 29Sep2022

Signed By	Date (GMT)
PPD	30-Sep-2022 14:51:53
Approved-PPD	
PPD	30-Sep-2022 14:58:29
Approved-PPD	

--- Do Not Detach This Signature Page ---