CLINICAL STUDY PROTOCOL

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
Short Title:	VEGF-B Blockade with the Monoclonal Antibody CSL346 in Subjects with Diabetic Kidney Disease
Sponsor:	CSL Behring LLC 1020 First Avenue King of Prussia, Pennsylvania 19406 United States of America
Protocol Version:	Amendment 2
IND Number:	145352
Protocol Date:	27 May 2021
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation), ethical principles that have their origin in the Declaration of Helsinki, and all applicable national and local regulations.

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

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

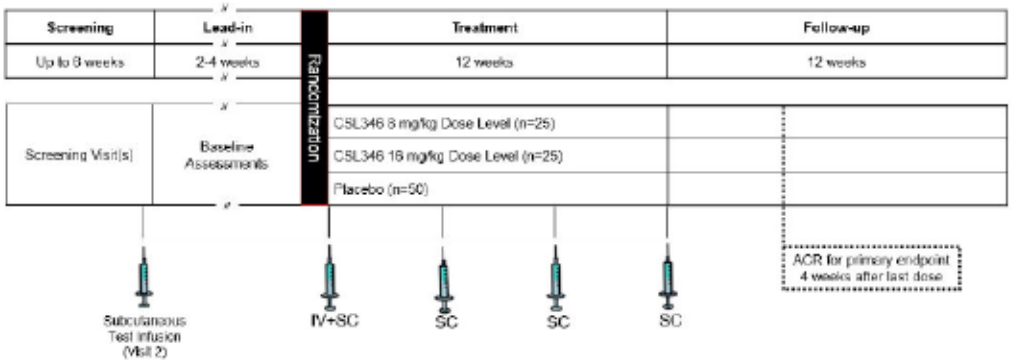
REVISION HISTORY

Date	Version	Summary of Changes
16 January 2020	Original	Not applicable
07 May 2020	Amendment 1	• Added a higher dose of CSL346 in CSL346 treatment arm and updated dose rationale • Updated randomization scheme • Updated statistical analyses of primary and secondary endpoints and added further exploratory analyses • Increased dose volumes and infusion durations • Added dose level stopping criteria • Added injection site reaction as an adverse event of special interest • Provided guidance for administration and dose adjustments for mild injection site reactions • Updated sample size estimation and added allowance for an increase in sample size of up to 124 subjects if there is a higher than expected drop-out rate • Added and revised further exploratory pharmacodynamic biomarkers • Added immunosuppressants as a prohibited concomitant therapy • Revised lifestyle restrictions (described contraceptive barrier method and adjusted alcohol limits) • Made editorial revisions, where applicable
27 May 2021	Amendment 2	• Added potential inclusion of subjects with estimated glomerular filtration rate between > 20 and < 45 mL/min/1.73m^2 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 clarification for use of antihypertensives • Added Screened Analysis Set • Added Interim Analysis for decision making • Added clarification for women of childbearing potential or males with partners of childbearing potential • Made editorial revisions, where applicable

Clinical Study Protocol Synopsis

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
Sponsor	CSL Behring LLC
Development Phase	2a
Study Product	CSL346 (vascular endothelial growth factor [VEGF]-B antagonist mAb)
Indication	Diabetic kidney disease (DKD)
Study Summary and Overview	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 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:



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 12 weeks of approximately monthly (every 4 weeks) administration of investigational product (IP). Using an interactive response technology system, eligible subjects will be randomized (1:1:2) to receive blinded IP (8 mg/kg CSL346, 16 mg/kg CSL346, or placebo).

Each subject's first dose of IP at Visit 4 (Day 1) will be an intravenous (IV) loading dose of 3 mg/kg CSL346 (subjects randomized to 8 mg/kg CSL346), 6 mg/kg CSL346 (subjects randomized to 16 mg/kg CSL346), or placebo (subjects randomized to placebo). All IV loading doses will be in a total volume of 10 mL and will be infused over the course of approximately 20 minutes. The subject will then be monitored for approximately 2 hours, during which adverse events (AEs) and vital signs will be recorded periodically as described in the Schedule of Assessments. If no clinically relevant AEs are observed during this time, the subject's first SC dose of IP will be administered as an 8 mg/kg, 16 mg/kg, or placebo 20 mL SC infusion over the course of approximately 40 minutes.

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.

Guidance is provided for adverse events of special interest (AESIs): injection site reactions; increase in serum creatinine (SCr), albuminuria, or blood pressure (BP); and cardiac-related AEs.

Dose and / or administration adjustments are permitted for mild injection site reactions that are deemed unacceptable and would otherwise lead to discontinuation of the IP.

Relevant unblinded data from all subjects participating in the study will be reviewed by the Independent Data Monitoring Committee

	(IDMC) during regularly-scheduled safety and PK reviews, as detailed in the IDMC Charter. *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.
Primary Objective	The primary objective of this study is to evaluate the efficacy of CSL346 administered every 4 weeks for 12 weeks (4 doses) in subjects with DKD.
Primary Endpoint	Change in log-transformed urinary albumin-to-creatinine ratio (ACR) from Baseline to Week 16 (Visit 10)
Secondary Objectives	The secondary objectives of this study are as follows: 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 SCr concentration and eGFR in subjects with DKD 3. To evaluate the effect of CSL346 on 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
Secondary Endpoints	The secondary endpoints of this study are as follows: 1. Treatment-emergent adverse events, including AESIs, from the time of first dose of IP through End of Study (EOS) 2. Observed value and change from Baseline in SCr and eGFR through EOS 3. Observed value and change from Baseline in systolic and diastolic BP through EOS 4. 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} after first SC dose, area under the concentration-time curve in first dosing interval ($AUC_{0-\tau}$), and trough concentration (C_{trough}) after each dose 5. Presence of anti-drug antibodies at Week 4 (Visit 7), Week 8 (Visit 8), and Week 16 (Visit 10)

Exploratory Objectives	The exploratory objectives of this study are as follows: 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 (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
Exploratory Endpoints	The exploratory endpoints for this study are as follows: 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, low density lipoproteins, glycerol, non-esterified fatty acids, and ketones • Biomarkers of glycemic control including, but not limited to, fasting glucose and hemoglobin A1c (HbA1c) • Novel biomarkers including, but not limited to, serum-free VEGF-B and soluble tumor necrosis factor receptor-1 and urinary VEGF-A, soluble VEGF receptor 1(VEGF-R1), kidney injury molecule -1, neutrophil gelatinase-associated lipocalin, 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 subjects who regress from macroalbuminuria to microalbuminuria or normoalbuminuria, or from microalbuminuria to normoalbuminuria at Week 16 (Visit 10) compared to Baseline

Study Duration	The duration of the study for an individual subject is expected to be up to approximately 34 weeks. This estimate is based on the following: • An up to 6-week Screening Period • An up to 4-week Lead-in Period • A 12-week Treatment Period • A 12-week Follow-up Period The overall study duration (ie, first subject's Screening Visit to last subject's EOS Visit) will be approximately 22 months.
Number of Subjects	The study will randomize a target of 100 subjects: • 25 subjects randomized to the 8 mg/kg CSL346 group • 25 subjects randomized to the 16 mg/kg CSL346 group • 50 subjects randomized to the placebo group A subject is considered enrolled in the study once they have signed the informed consent form. A subject is considered eligible for randomization into the study when all inclusion criteria have been met, none of the exclusion criteria have been met, and the randomization criteria have been met. 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).
Study Population and Main Criteria for Eligibility	*Inclusion* The study will enroll male and female subjects ≥ 25 years of age with a diagnosis of type 2 diabetes mellitus. Subjects must have a urinary ACR ≥ 150 mg/g (16.95 mg/mmol) from a 24-hour timed urine collection. The initial study population must have eGFR ≥ 60 mL/min/1.73m^2 and glycosylated HbA1c < 12%. After an IDMC review of safety and PK data from the first 18 subjects with eGFR ≥ 60 mL/min/1.73m^2, inclusion of subjects with eGFR ≥ 45 mL/min/1.73m^2 (including chronic kidney disease stage 3A) will be permitted if approved by the IDMC. Subsequently, after an IDMC review of safety and PK data from the first 36 subjects (at least 8 subjects with eGFR ≥ 45 to < 60 mL/min/1.73m^2) followed for at least 4 weeks, inclusion of subjects with eGFR > 20

	to < 45 mL/min/1.73m^2 will be permitted if approved by the IDMC. If inclusion of subjects with eGFR below 60 mL/min/1.73m^2 is endorsed by the IDMC, the following target sample size(s) will be established for subjects with eGFR in the specified range: • At least 36 subjects with eGFR < 60 mL/min/1.73m^2 • At least 18 subjects with eGFR < 45 mL/min/1.73m^2 To achieve these targeted minimums, a restriction may be imposed on the enrollment of subjects with eGFR ≥ 60 mL/min/1.73m^2 and / or ≥ 45 mL/min/1.73m^2. Subjects must have been taking stable doses of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy for at least 8 weeks before Screening. Subjects taking antihypertensive medication(s) must have been taking stable doses for at least 8 weeks before Screening. Every effort will be made to ensure that at least 50% of randomized subjects are receiving concomitant treatment with a sodium-glucose cotransporter 2 inhibitor (dose stable for at least 4 weeks before Screening). *Exclusion* Subjects must not have a current diagnosis of type 1 diabetes mellitus, history of acute kidney injury or chronic dialysis/renal transplant, anticipated renal transplant, uncontrolled hypertension or Class III / IV heart failure, left ventricular ejection fraction < 50% by echocardiogram, troponin-I > the upper reference limit, b-type natriuretic peptide (BNP) > 200 pg/mL, or alanine transaminase > 2x the upper limit of normal.
Study Product Dose, Dosing Regimen, and Administration	CSL346 is supplied as a sterile solution for IV and SC infusion at a concentration of 100 mg/mL. All CSL346 doses will be calculated based on weight and normalized to a standard volume with sterile normal saline. CSL346 will be administered at an initial 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.

Comparator Product, Dose, Dosing Regimen, and Administration	Placebo consists of normal saline for IV and SC infusion. Dosing administration, regimen, and volume will be matched to CSL346.
Efficacy Assessments	The efficacy of CSL346 will be assessed based on changes in ACR associated with CSL346 treatment. To minimize intrasubject variability, baseline values for these parameters will be based on the geometric mean values from 3 first morning void (FMV) urine collections on 2 separate occasions (ie, 6 total FMV samples) before the first dose of IP. On-treatment assessments of ACR will be the geometric mean values from multiple FMV collections at each time point. Only 2 FMV samples will be collected at Visit 9 because a timed 24-hour sample will also be collected at this Visit. The Follow-up assessment of ACR performed for the primary analysis 4 weeks after the last dose of IP (Visit 10) will be based on the geometric mean of 3 FMV samples. For the EOS Visit, the assessment of ACR will also be based on the geometric mean of 3 FMV samples.
Safety Assessments	The safety and tolerability of CSL346 will be based on the following: • AEs (including AESIs) • Vital signs • Physical examinations • 12-lead electrocardiograms • Clinical laboratory assessments (urinalysis, hematology, biochemistry, troponin-I, BNP, SCr, and eGFR)
Pharmacokinetics	Serial blood samples for the determination of CSL346 concentration will be collected at Visit 4 (Day 1). Single PK samples will also be collected at all subsequent visits (before treatment on SC dosing days).
Exploratory Assessments	*Biomarkers of Lipid Metabolism* Fasting blood samples for the determination of serum glycerol, non-esterified fatty acids, and ketones will be collected at Visit 3 (Day -7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16). Fasting blood samples for the determination of total cholesterol, triglycerides, high density lipoprotein, and low density lipoprotein levels will also be collected at Visit 3 (Day -7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10

(Week 16) as part of the standard biochemistry panel.

Biomarkers of Glycemic Control

Blood samples for the determination of HbA1c levels will be collected at Screening (Visit 1), Visit 4 (Day 1), Visit 10 (Week 16) and EOS. Blood samples for the determination of fasting glucose levels will be collected at Visit 3 (Day -7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16) as part of the standard biochemistry panel.

Novel Plasma, Serum, and Urinary Biomarkers

Fasting blood samples for the determination of serum free VEGF-B and soluble tumor necrosis factor receptor-1 levels will be collected at Visit 3 (Day -7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16).

Urine samples for the determination of VEGF-A, soluble VEGF-R1, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, clusterin, and monocyte chemoattractant protein-1 will be collected at Visit 3 (Day -7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16).

CSL346 in Urine (PK)

Timed 24-hour urine samples for the determination of CSL346 concentration will be collected at Screening (Visit 1, Baseline), Visit 5 (Week 1), and Visit 9 (Week 12).

ACR

As an exploratory assessment, the data generated for the primary analysis will also be used to evaluate changes in clinical characterization of albuminuria: normoalbuminuria, microalbuminuria, or macroalbuminuria.

To do this, each subject's level of urinary ACR (average of available FMV samples at each time point) will be categorized at Baseline and at Visit 10 (Week 16) as:

- Macroalbuminuria (ACR > 300 mg/g [> 33.9 mg/mmol])
- Microalbuminuria (ACR ≥ 30 and ≤ 300 mg/g [≥ 3.39 and ≤ 33.9 mg/mmol]), or
- Normoalbuminuria (ACR < 30 mg/g [< 3.39 mg/mmol])

	Transitions between these categories will be described.
Statistical Analyses	*Sample Size* 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 an 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, ie, ln (1 to 0.27) = -0.315 on the natural log scale, using a one-sided alpha = 0.10. The total sample size 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). *Primary Endpoint 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 primary comparison of interest is a contrast of 0.5 (8 mg/kg CSL346 + 16 mg/kg CSL346) – Placebo. 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 (ie, 4 weeks after the fourth dose). These results will be summarized in an interim, nonregulatory, analytical report. 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. *Secondary Endpoint Analyses* Treatment-emergent AEs, defined as AEs occurring at or after the start of study treatment, will be summarized for each CSL346 dose level (8 mg/kg and 16 mg/kg) and placebo. An overview summary of AEs, including the number of subjects with any AE; AEs related to study treatment; AEs leading to discontinuation of study treatment; serious adverse events; and deaths will be produced. Treatment-emergent AEs will be summarized by preferred term and

system organ class as well as severity. AESIs will also be summarized separately.

The analysis of SCr, eGFR, and BP will employ a model similar to the primary endpoint. The analysis for these continuous endpoints is an MMRM analysis of change from Baseline to each post-baseline measurement.

Serum concentration of CSL346 will be listed by individual subject and will be summarized by dose level and nominal time point using descriptive statistics (ie, n, arithmetic mean, SD, coefficient of variation [CV%], median, geometric mean, geometric CV%, minimum, and maximum). Individual subject CSL346 serum concentration versus time will be plotted on linear and semi-logarithmic scales. The C_{trough} of CSL346 will also be summarized visually, by dose level.

The number of subjects with a positive immunogenicity test at any time post-treatment will be counted and compared between treatments with Fisher's Exact Test. The comparison will be of CSL346 (8 mg/kg and 16 mg/kg pooled) versus placebo.

Exploratory Endpoint Analyses

Exploratory endpoints will employ a model similar to the primary endpoint and continuous secondary endpoints. The analysis for these continuous endpoints is an MMRM analysis of change from Baseline to each post-baseline measurement. Exploratory urinary biomarkers will be normalized to creatinine level for analysis and reporting. The number of subjects who regress from macroalbuminuria to microalbuminuria or normoalbuminuria, or from microalbuminuria to normoalbuminuria at Week 16 will be counted and compared between treatments using Fisher's Exact Test. The comparison will be of CSL346 (8 mg/kg and 16 mg/kg pooled) versus placebo.

Data from the exploratory biomarkers will be summarized descriptively by treatment and visit for the PD Analysis Set.

Pharmacokinetic and PD endpoints will be explored graphically to evaluate potential relationships.

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	
SC normal saline test infusion		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
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; IP = investigational product; IRT = interactive response technology; IV = intravenous; NA = not applicable; PK = pharmacokinetic; SC = subcutaneous; PT = prothrombin time.

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 (see Section 4.1.3 for detailed guidance).

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), body temperature, and pulse rate. 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).

O: 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.

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List of Abbreviations

Abbreviation	Term
ACEi	Angiotensin-converting enzyme inhibitor
ACR	Albumin-to-creatinine ratio
AE	Adverse event
AESI	Adverse events of special interest
AKI	Acute kidney injury
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	antibody to hepatitis B surface antigen
ARB	Angiotensin II receptor blocker
AUC	Area under the concentration-time curve
$AUC_{0\text{-}28d\_ss}$	AUC between doses at steady state where dosing interval (τ) = 28 days (4 weeks)
$AUC_{0\text{-}\tau}$	Area under the concentration-time curve in a dosing interval
$AUC_{0\text{-}\infty}$	AUC from time 0 to infinity
BP	Blood pressure
BNP	B-type natriuretic peptide
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum concentration
COVID-19	Novel coronavirus 2019
CSL	CSL Behring LLC
cTnI	Cardiac troponin-I
CTRA	Clinical Trial Research Agreement
C_{trough}	Trough concentration
C_{trough_ss}	Trough concentrations at steady state
CV	Coefficient of variation (%)
DBP	Diastolic blood pressure
DKD	Diabetic kidney disease
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
ECHO	Echocardiogram

Abbreviation	Term
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of study
FCBP	Female subjects of childbearing potential
FDA	Food and Drug Administration
FMV	First morning void
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HDL	High density lipoproteins
HFD	High-fat diet (mouse model)
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product (Handing Manual)
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intention-to-Treat
IV	Intravenous
LVEF	Left ventricular ejection fraction
MMRM	Mixed effects model, repeated measures
NEFA	Non-esterified fatty acids
PD	Pharmacodynamic
PK	Pharmacokinetic
RAS	Renin angiotensin system
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation	Term
SBP	Systolic blood pressure
SC	Subcutaneous
SCr	Serum creatinine
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter 2
SOC	Standard of care
T2DM	Type 2 diabetes mellitus
T_{max}	Time to reach maximum concentration in serum
ULN	Upper limit of normal
URL	Upper reference limit
VEGF	Vascular endothelial growth factor

1 Introduction

1.1 Background

Diabetic kidney disease (DKD) is the most common cause of end stage renal disease and its prevalence continues to grow worldwide [GBD 2018]. Diabetic kidney disease is first detected by the abnormal loss of small amounts of albumin into the urine (microalbuminuria). As DKD progresses with increasingly larger losses of urinary albumin, renal function declines leading to chronic kidney disease (CKD) and the eventual initiation of renal replacement therapy. The standard of care (SOC) to slow the decline in renal function in patients with DKD has consisted of glycemic control, use of renin angiotensin system (RAS) inhibitors, and management of hypertension and hyperlipidemia [KDOQI, 2007 and 2012]. The SOC is expected to evolve over the next few years to include the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors [Perkovic et al, 2019; Sarafidis et al, 2019; Garber et al, 2019]. Nevertheless, treatment with both RAS and SGLT2 inhibitors does not arrest or reverse the progression of DKD [Khan and Quaggin, 2015; Perkovic et al, 2019]. Worldwide, over 300,000 patients with DKD progress to end stage kidney disease requiring dialysis or renal transplant each year. Thus, additional treatment options are needed to preserve renal function.

Vascular endothelial growth factor (VEGF)-B primarily regulates fatty acid transport across the endothelium [Hagberg et al, 2010], whereas other members of the VEGF family stimulate de novo growth of blood vessels (ie, angiogenesis; VEGF-A and placental growth factor, to a lesser extent) or lymphatic vessels (ie, lymphangiogenesis; VEGF-C and -D). In DKD, VEGF-B expression in the diabetic kidney (murine and human) is elevated and associated with increased lipid deposition in glomerular podocytes as free fatty acids are shunted from adipose tissue (murine) [Falkevall et al, 2017]. The DKD phenotype is observed in podocyte-specific VEGF-B overexpressing mice [Falkevall et al, 2017]. Reducing VEGF-B activity in mouse models of type 1 diabetes mellitus (streptozotocin-induced diabetes) and type 2 diabetes mellitus (T2DM, *db*/*db*, or high-fat diet [HFD]-induced)-DKD with an anti-VEGF-B antibody results in improvement of histological evidence of glomerular injury and reduces albuminuria [Falkevall et al, 2017]. The beneficial effects of blocking VEGF-B activity have been attributed to the prevention of toxic lipid accumulation in the kidney. A molecule that antagonizes VEGF-B activity has the potential to slow the rate of loss of renal function via pathways other than those impacted by either RAS or SGLT2 inhibition.

1.2 Information on CSL346

1.2.1 Overview

CSL346 is a novel humanized monoclonal antibody (immunoglobulin G 4) derived from the murine variant anti-VEGF-B antibody known as 2H10. CSL346 binds with high affinity to VEGF-B, which is expected to result in improvement of DKD with minimal off-target effects.

A detailed description of the chemistry, pharmacology, efficacy, and safety of CSL346 is provided in the Investigator's Brochure.

1.2.2 Nonclinical Evaluation

In CSL346 repeat-dose toxicity studies of up to a 6-month duration, there were no adverse events (AEs), including injection site reactions, observed up to the highest dose tested, 100 mg/kg, administered by intravenous (IV) or by subcutaneous (SC) injection. These data are supportive of administering repeat doses up to 16 mg/kg SC to subjects in clinical studies.

A detailed description of the nonclinical data available for CSL346 is provided in the Investigator's Brochure and Addendum.

1.2.3 Clinical Experience

The first in-human clinical study, CSL346_1001, a phase 1, randomized, double-blind, placebo-controlled single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics (PK) of CSL346 in healthy Caucasian and Japanese adult subjects was completed in May 2019. Overall, no AEs of concern occurred following administration of single doses of CSL346 by an IV infusion (up to 20 mg/kg) or SC injection (up to 10 mg/kg) to 60 healthy volunteers, thus demonstrating safety and tolerability up to the maximum exposures achieved. The PK profile suggests dose proportionality and, as expected, is similar in Caucasian and Japanese subjects. The bioavailability after SC administration is estimated to be 61% in healthy volunteers. This study is supportive of continued development of CSL346, including administration of repeat doses of up to 16 mg/kg SC to subjects with DKD.

A detailed description of the safety and PK profile of CSL346 in healthy adult subjects is provided in the Investigator's Brochure.

1.3 Study Overview

This is a prospective, multicenter, randomized, double-blind, placebo-controlled, proof of concept study to investigate the efficacy, safety, tolerability, and PK of repeat doses of CSL346 in subjects with DKD and albuminuria receiving SOC treatment. Approximately 100 subjects will be randomized (1:1:2) to receive 8 mg/kg CSL346, 16 mg/kg CSL346, or placebo and participate for up to 34 weeks. Section 3.1 provides a detailed overview of the study.

1.4 Potential Risks and Benefits

Benefits: Subjects in clinical studies generally cannot expect to receive direct benefit from treatments during participation, as clinical studies are designed to provide information about safety and efficacy of a new investigational product (IP). However, benefits may include the following:

1. Opportunity to contribute to the understanding of potential new treatment for DKD
2. Potential improvements in clinically important markers associated with DKD
3. Close medical evaluation and study-related medication and procedures

Risks: Risks identified to date in nonclinical and clinical investigations of CSL346 are nonserious injection site reactions with SC dosing. In the nonclinical toxicology studies with up to 6 months of dosing administered IV or by SC injection, no dose-limiting toxicity was seen up to the highest dose tested. There were no dose-limiting toxicities in the single ascending dose study in healthy volunteers, and the most common AEs reported across the 3 study parts were upper respiratory infection (Part A and Part B), headache (Part A and Part C), and injection site pain (Part C).
Administration of therapeutic proteins, including monoclonal antibodies such as CSL346, is associated with the risk of hypersensitivity and anaphylactic reactions, some of which can be serious and life-threatening. Appropriate precautions will be taken during CSL346 administration, with vigilant monitoring for potential anaphylactic reactions and treatment according to SOC. The initial administrations of CSL346 will be performed under medical supervision, and subjects will be advised to seek medical attention if delayed reactions occur after discharge from the site.

Additional safety monitoring and / or risk mitigation implemented for this study will include antidrug antibody development, weight gain, and congenital disorders.

Due to the potential for VEGF-B antagonism to modulate VEGF-A tone, adverse effects on renal and cardiac parameters known to occur in patients with metastatic cancer treated with anti-VEGF-A agents were also considered.

Subjects will have enhanced safety monitoring over the 4 weeks following their first exposure to blinded IP and before administration of the second SC dose at Week 4 (Visit 7). This includes frequent blood pressure (BP) monitoring at Visit 4 (Day 1) and study visits at Week 1 (Visit 5) and Week 2 (Visit 6).

An overview of identified and potential risks and planned risk mitigation in this phase 2a study is provided in Table 1.

Table 1 Risks and Risk Mitigation

Risk	Potential/ Identified	Source	Risk Mitigation
Injection site reactions	Identified	CSL346_1001 data on file	• Assessment at study visits • Guidance for managing local intolerance
Hypersensitivity / anaphylaxis and infusion reactions; antibody formation	Potential	Class effect of humanized proteins	• Standard measures • Measurement of baseline, mid-, and end of study anti-CSL346 antibody
Weight gain	Potential	Knock-out mouse model [Hagberg et al, 2010]	• Monitor at study visits
Congenital disorders	Potential	Knock-out mouse model [Bellomo et al, 2000] Preclinical study in quails [Tomanek et al, 2006]	• Inclusion / exclusion criteria • Contraception requirements • Pregnancy testing • Nonclinical studies in later phases
Renal: acute reversible effect on GFR and / or chronic kidney injury	Potential	Theoretical risk due to VEGF-A modulation [Kamarzarian et al, 2018; Izzedine et al, 2010]	• Inclusion / exclusion criteria • Staged approach for enrollment of subjects with moderate renal impairment • Frequent monitoring in first 4 weeks of treatment • Measure SCr and evaluate albuminuria at each visit • Guidance for managing increases in SCr and albuminuria

Risk	Potential/ Identified	Source	Risk Mitigation
Cardiac: myocardial dysfunction with chronic dosing	Potential	Knock-out mouse model [Bellomo et al, 2000] Streptozotocin model [Lal et al, 2017] Theoretical risk due to VEGF-A modulation [Touyz et al, 2018]	• Exclusion criteria, including baseline assessment of LVEF by ECHO • Treatment with SOC • Baseline and periodic ECG, BNP, and troponin levels • Guidance for managing increases in troponin levels
Increased BP	Potential	Theoretical risk due to VEGF-A modulation [Touyz et al, 2018]	• Exclusion criteria • BP measurement • Guidance for managing increases in BP

BP = blood pressure; BNP = b-type natriuretic peptide; ECG = electrocardiogram; ECHO = echocardiogram; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; SCr = serum creatinine; SOC = standard of care; VEGF = vascular endothelial growth factor.

2 Study Objectives and Endpoints

2.1 Primary Objective and Endpoint

2.1.1 Primary Objective

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

2.1.2 Primary Endpoint

Endpoint	Summary Measure
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 (95% CI), expressed as percent change from Baseline

2.2 Secondary Objectives and Endpoints

2.2.1 Secondary Objectives

The secondary objectives of this study are as follows:

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 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

2.2.2 Secondary Endpoints

Secondary Objective	Endpoint	Summary Measure
1	Treatment-emergent adverse events, including adverse events of special interest (AESIs) from the time of first dose of the IP through End of Study (EOS)	Number and percentage of subjects overall, by severity, by relatedness, by seriousness, and by action (ie, IP discontinuation)
2	Observed value and change from Baseline in SCr and eGFR through EOS	Mean (SD)
3	Observed value and change from Baseline in systolic and diastolic blood pressure (SBP and DBP) through EOS	Mean (SD)
4	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 ($AUC_{0-\tau}$) • Trough concentration (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}
5	Presence of anti-drug antibody 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)

2.3 Exploratory Objectives and Endpoints

2.3.1 Exploratory Objectives

The exploratory objectives of this study are:

1. To explore the effect of CSL346 on the following potential pharmacodynamic (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 (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

2.3.2 Exploratory Endpoints

The exploratory endpoints for this study are as follows:

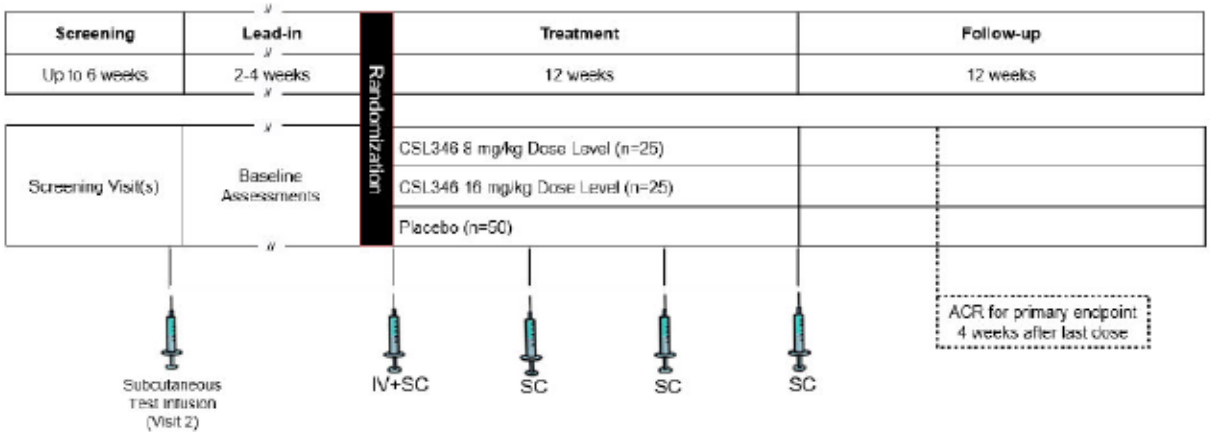
1. Changes from Baseline to each assessment in fasting values for the following PD biomarkers:
   - Biomarkers of lipid metabolism including, but not limited to, circulating total cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, glycerol, non-esterified fatty acids, and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

3 Study Design and Oversight

3.1 Overall Design

This is a prospective, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study to investigate the efficacy, safety, tolerability, and PK of repeat doses of CSL346 in subjects with DKD and albuminuria receiving SOC treatment. The study will be divided into 4 periods: Screening, Lead-in, Treatment, and Follow-up (Figure 1).

Figure 1 Overall Study Design



ACR = albumin-to-creatinine ratio; IV = intravenous; SC = subcutaneous.

Approximately 100 subjects will be randomized (1:1:2) to receive blinded IP (8 mg/kg CSL346, 16 mg/kg CSL346, or placebo) for 12 weeks. The initial study population will include subjects with T2DM-DKD and preserved renal function (eGFR $\geq$ 60 mL/min/1.73m^2); the first 18 subjects randomized will be followed for at least 4 weeks after their first dose of IP (Visit 4, Day 1), at which point an Independent Data Monitoring Committee (IDMC) will review their safety and PK data. Following this review, inclusion of subjects with eGFR $\geq$ 45 mL/min/1.73m^2 (including CKD stage 3A) will be permitted if approved by the IDMC.

Subsequently, after an IDMC review of safety and PK data from the first 36 subjects (at least 8 subjects with eGFR $\geq$ 45 to < 60 mL/min/1.73m^2) followed for at least 4 weeks, inclusion of subjects with eGFR > 20 to < 45 mL/min/1.73m^2 will be permitted if approved by the IDMC. If inclusion of subjects with eGFR below 60 mL/min/1.73m^2 is endorsed by the IDMC, the

following targeted sample size(s) will be established for subjects with eGFR in the specified range:

- At least 36 subjects with eGFR < 60 mL/min/1.73m^2
- At least 18 subjects with eGFR < 45 mL/min/1.73m^2

To achieve these targeted minimums, a restriction may be imposed on the enrollment of subjects with eGFR ≥ 60 mL/min/1.73m^2 and / or ≥ 45 mL/min/1.73m^2.

This staged approach to including subjects with increasing degrees of renal impairment (ie, eGFR ≥ 45 and eGFR > 20 mL/min/1.73m^2) is designed to mitigate risk to subjects while enabling preliminary assessment of safety and efficacy in the study population that increasingly reflects the target population for phase 3.

Subjects receiving CSL346 will be administered an initial loading dose of 3 mg/kg or 6 mg/kg IV, followed by 8 mg/kg or 16 mg/kg SC, respectively, 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. Subjects receiving placebo will be administered normal saline using a matched regimen and volume. The primary endpoint (ACR) will be assessed 4 weeks after the last dose of IP.

Study procedures will be conducted as described in the Schedule of Assessments.

3.1.1 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 and Exclusion Criteria (Section 4.1.1 and Section 4.1.2, respectively). Visit 2 must occur within 6 weeks after Visit 1. An SC test infusion is to be done at Visit 2 after subject eligibility has been confirmed (ie, assessment of results from Visit 1 and assessment of results available at the time of Visit 2) (see Section 8.2.1).

Screening assessments not satisfying inclusion criteria can be repeated within the 6-week Screening Period (signing of informed consent form [ICF] to Visit 2) if the Investigator has reason to believe the failed criteria(on) may have changed on repeat assessment.

- If the eligibility criteria(on) is met on the repeat assessment, the subject may proceed to the Lead-in Period
- If the eligibility criteria(on) is NOT met on the repeat assessment, the subject will be considered a screen failure (Section 4.2)

Re-screening of the subject is permitted once after a minimum 2-month interval between the initial Screening Visit and re-screening (signing informed consent document[s] for the re-screening period). During re-screening, the subject must have all screening procedures and assessments repeated to demonstrate eligibility for the study.

3.1.2 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 (Section 4.1.3). Assessments not satisfying the Randomization Criteria can be reassessed during the Lead-in Period if the Investigator has reason to believe the failed criteria(on) may have changed on repeat assessment. If all Randomization Criteria are satisfied, the subject will be eligible for randomization in the Treatment Period (Visit 4, Day 1).

3.1.3 Treatment Period

The Treatment Period will include 12 weeks of approximately monthly (every 4 weeks) administration of 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).

Each subject's first dose of IP at Visit 4 (Day 1) will be an IV loading dose of 3 mg/kg CSL346 (subjects randomized to 8 mg/kg CSL346), 6 mg/kg CSL346 (subjects randomized to 16 mg/kg CSL346), or placebo (subjects randomized to placebo). All IV loading doses will be in a total volume of 10 mL and infused over the course of approximately 20 minutes. The subject will then be monitored for approximately 2 hours, during which AEs and vital signs will be recorded periodically as described in the Schedule of Assessments and Section 8.1.1. If no clinically relevant AEs are observed during this time, the subject's first SC dose of IP will be administered as an 8 mg/kg CSL346, 16 mg/kg CSL346, or placebo 20 mL SC infusion over the course of approximately 40 minutes.

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.

3.1.4 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 PD parameters after stopping treatment.

Relevant unblinded data from all subjects participating in the study will be reviewed by the IDMC during regularly-scheduled safety reviews, as detailed in the IDMC Charter.

3.2 Dose and Dosing Regimen

At Visit 4 (Day 1), CSL346 will be administered at an initial loading dose of 3 mg/kg or 6 mg/kg IV, followed by 8 mg/kg or 16 mg/kg SC, respectively, 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.

Subjects experiencing a mild injection site reaction deemed unacceptable by the subject or Investigator may have administration and / or dose adjustments (see Section 5.1.3.1).

The IDMC will evaluate the need for dose de-escalation during planned reviews of emerging data (see Section 3.6.1) and may discontinue the 16 mg/kg CSL346 dose level as per predefined dose level stopping criteria (Section 3.7.2).

Placebo consists of normal saline for IV and SC infusion. Dosing administration, regimen, and volume will be matched to CSL346.

3.3 Scientific Rationale

3.3.1 Study Design Rationale

This is a phase 2a, randomized, double-blind, placebo-controlled study using a standard parallel-group study design. The initial population will include subjects with DKD due to T2DM and preserved renal function (eGFR $\geq$ 60 mL/min/1.73m^2) with a lower risk of renal and cardiovascular disease [Neuen et al, 2018]. Inclusion of subjects with eGFR $\geq$ 45 and $<$ 60 mL/min/1.73m^2 (CKD stage 3A) will be permitted if approved by the study's IDMC after reviewing safety and PK data from the first 18 subjects.

Subsequently, after an IDMC review of safety and PK data from the first 36 subjects (at least 8 with eGFR ≥ 45 to < 60 mL/min/1.73m^2) followed for at least 4 weeks, inclusion of subjects with eGFR > 20 to < 45 mL/min/1.73m^2 will be permitted if approved by the IDMC.

If inclusion of subjects with eGFR below 60 mL/min/1.73m^2 is endorsed by the IDMC, the following target sample size(s) will be established for subjects with eGFR in the specified range:

- At least 36 subjects with eGFR < 60 mL/min/1.73m^2
- At least 18 subjects with eGFR < 45 mL/min/1.73m^2

To achieve these targeted minimums, a restriction may be imposed on the enrollment of subjects with eGFR ≥ 60 mL/min/1.73m^2 and / or ≥ 45 mL/min/1.73m^2.

This staged approach to including subjects with increasing degrees of renal impairment (ie, eGFR ≥ 45 and eGFR > 20 mL/min/1.73m^2) is designed to mitigate risk to subjects while enabling preliminary assessment of safety and efficacy in the study population that increasingly reflects the target population for phase 3.

Two doses of CSL346 will be assessed to increase the likelihood of showing a treatment effect, assessing tolerability and to generate additional PK / PD data for dose selection in subsequent trials. Criteria for dose de-escalation are in place.

Urinary ACR is an established renal surrogate biomarker in this patient population and has therefore been selected to evaluate efficacy for the primary objective [Coresh et al, 2019; Heerspink et al, 2019]. To minimize variability and optimize the ability to interpret the results, medications used for glycemic control and the treatment of DKD (eg, RAS inhibitors and SGLT2 inhibitors) must be stable before study enrollment. In addition, multiple, consecutive first morning void (FMV) urine collections at each time point will be used for ACR analysis [Kröpelin et al, 2015]. These samples will be collected at Baseline, periodically during the Treatment Period and at the end of the Treatment Period, and during the Follow-up Period. Based on results from studies conducted in standard animal DKD models, 12 weeks of dosing is highly likely to demonstrate ACR activity in a clinical study. The 12-week duration of the Follow-up Period was determined based on the extended half-life of CSL346 and enables characterization of the treatment effect while exposure declines.

3.3.2 Dose Rationale

Doses were selected based on the expected effect of CSL346 in subjects with DKD. In the absence of safety or toxicity findings and PD data from Study CSL346_1001, bridging of PK from healthy volunteers to subjects with DKD was based on population PK modelling of data in healthy volunteers along with PK / PD data from mouse models of T2DM-DKD (HFD and *db*/*db*). Proposed doses and regimen were selected to assess pharmacological activity (eg, changes in albuminuria) in subjects with T2DM-DKD. Pharmacokinetic data from *db*/*db* mice treated with a pharmacologically active dose of 2H10, the murine version of CSL346, was used to identify a threshold target concentration of CSL346 predicted to provide pharmacological activity in subjects with DKD.

The PK profile in healthy subjects enrolled in Study CSL346_1001, administered single doses of CSL346 up to 20 mg/kg by IV infusion or up to 10 mg/kg by SC injection, was dose proportional. Nonlinear mixed effects modelling of these data in healthy volunteers was used to establish the human population PK model. Weight was evaluated for its influence on the PK of CSL346, with no significant effects found in the healthy population. As preliminary data indicate that PK exposures between healthy mice and *db*/*db* mice of the same strain administered 2H10 are within 2-fold, dose adjustments for different levels of renal function were determined not to be required. This will be further evaluated by including subject data from this study.

Selection of the low dose was based on the expected clinical effect of CSL346 on albuminuria in the absence of any safety concerns in healthy subjects or nonclinical toxicity findings. Results from an HFD mouse model of DKD showed that twice weekly dosing of both 1 mg/kg and 10 mg/kg 2H10 prevented the increase of albuminuria over 20 weeks. Results from another study, using the *db*/*db* model of DKD, also showed that twice weekly dosing of 10 mg/kg 2H10 ameliorated albuminuria over 10 weeks. The dose for phase 2a was predicted from the PK / PD data using 10 mg/kg, as this dose had the greatest and most replicable effect on albuminuria in DKD mouse models. Serum C_{trough} of 2H10 at steady state (approximately 4 days after the last week of 11 weeks of twice weekly dosing) in *db*/*db* model mice treated with a 10 mg/kg dose of 2H10 twice weekly averaged 180 µg/mL.

Differences in potency between the mouse 2H10 antibody and CSL346 were calculated using data from a cell-based assay of VEGF-R1 activity [Mould et al, 2005]. The half maximal inhibitory concentrations of 2H10 in the presence of mouse VEGF-B (20 nM) and of CSL346 in the presence of human VEGF-B (1.25 nM) were 3 nM and 0.18 nM, respectively. The ratio

of these values (16.7) was used to correct for the observed effective concentration of 2H10 in mice and predict a target C_{trough} of CSL346 in humans. With the 16.7 adjustment for potency, a target CSL346 C_{trough} of 11 µg/mL was calculated. In a direct binding enzyme-linked immunosorbent assay, the half maximal effective concentration (EC_{50}) of 2H10 on 1 µg/mL mouse VEGF-B was 3.21 nM and the EC_{50} of CSL346 on 1 µg/mL human VEGF-B was 0.257 nM. When using the ratio of these values (12.5) to correct for the concentration in mice, a target C_{trough} of 14.4 µg/mL was calculated. Selection of the doses was based on the 14.4 µg/mL target C_{trough}, as the direct binding assay provides a more accurate measure.

Considering the prolonged half-life (approximately 30 days), up to 5 months of monthly administration would be required to reach steady state with SC administration. Therefore, a single loading dose will be administered by IV infusion on Day 1 (Visit 4), followed by an SC infusion on Day 1 (Visit 4) to reach approximate steady state CSL346 concentrations earlier in the Treatment Period. To maintain target serum concentrations, IP will be administered by SC infusion every 4 weeks thereafter.

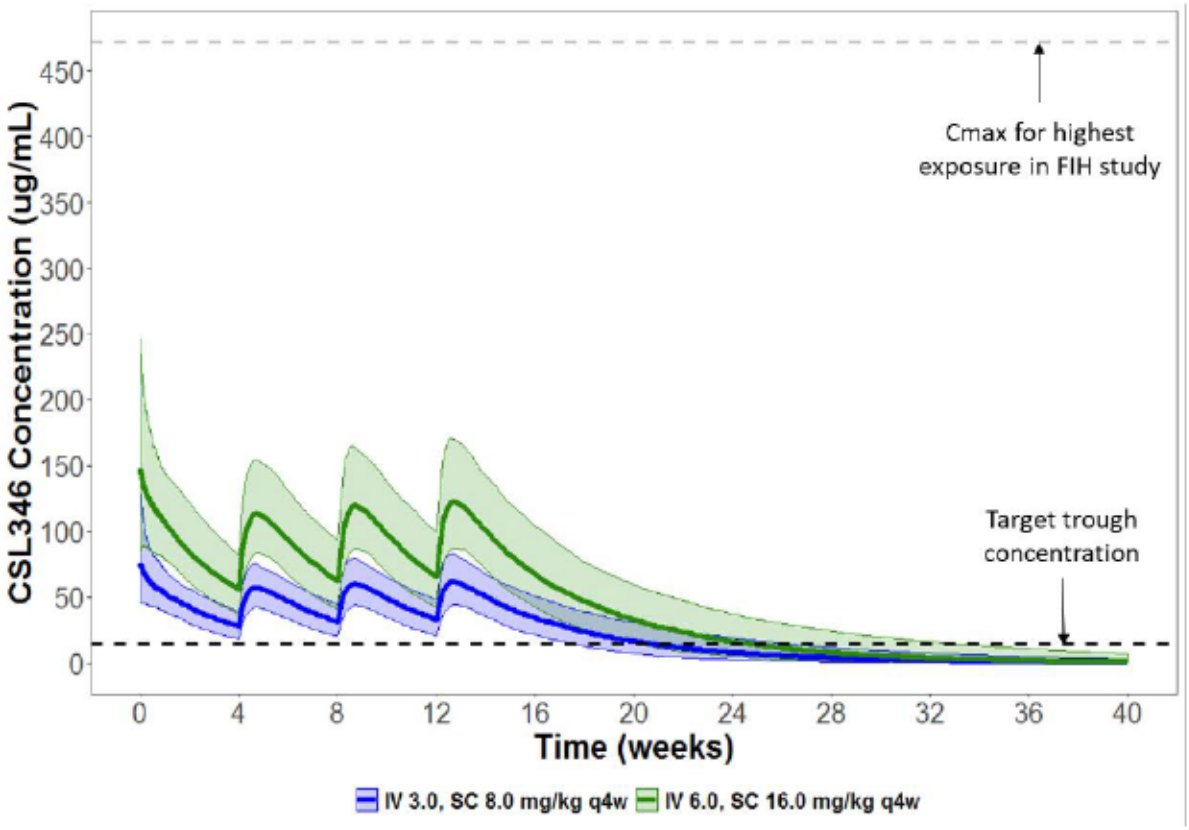
For the low dose, a loading dose of 3 mg/kg IV, followed by administration of 8 mg/kg SC on Day 1 (Visit 4) and every 4 weeks thereafter, was selected. Trough concentrations at steady state (C_{trough_ss}) are predicted to exceed 14.4 µg/mL in 99.9% of subjects treated with 8 mg/kg through Week 16 (Visit 10) (Figure 2). Predicted median (95% CI) area under the concentration-time curve $(AUC)_{0\text{-}28d\_ss}$ (AUC between doses at steady state where dosing interval [τ] = 28 days [4 weeks]) following repeat dosing of 8 mg/kg SC is 1336 (970 to 1921) µg•day/mL. This exposure is approximately 4.4- (6.0- to 3.0-) fold lower than the mean $AUC_{0\text{-}\infty}$ (AUC from time 0 to infinity) exposure after 12 weeks of follow up in healthy volunteers administered a single 20 mg/kg dose (5839 µg•day/mL) in Study CSL346_1001 (Table 2).

Selection of the high dose was based on the uncertainties of translation of mouse disease models to humans and the lack of quantitative data on VEGF-B levels in human tissues or a validated PD marker. Including a 2-fold higher dose allows for higher local exposure in the kidney and thus, an increased likelihood to observe efficacy in this proof of concept study in case activity is driven by local tissue concentrations of VEGF-B and CSL346 rather than systemic exposure. Additionally, the dose-response relationship across these 2 dose levels will help inform dose selection for a phase 2b dose-finding study.

For this high dose, a loading dose of 6 mg/kg IV will be followed by 16 mg/kg SC on Day 1 (Visit 4) and every 4 weeks thereafter. Following repeat dosing at the high dose of 16 mg/kg,

median (95% CI) $AUC_{0\text{-}28d\_ss}$ is predicted to be 2770 (1931 to 3815) µg•day/mL. This exposure is approximately 2.1 (3.0 to 1.5) fold lower than the mean $AUC_{0\text{-}\infty}$ exposure after 12 weeks of follow up in healthy volunteers administered a single 20 mg/kg dose (5839 µg•day/mL) in Study CSL346_1001 (Table 2). The trough concentrations at steady state (C_{trough_ss}) in subjects treated with 16 mg/kg CSL346 is predicted to exceed 14.4 µg/mL in all (ie, 100%) subjects at Week 16 (Visit 10) and in 59% of subjects at Week 24 (Visit 11) (Figure 2).

Figure 2 **Predicted CSL346 Concentrations Following Monthly SC Dosing with IV Loading Dose**



C_{max} = maximum concentration; FIH = first in human; IV = intravenous; q4w = once every 4 weeks; SC = subcutaneous.

Solid lines show the median of 1000 simulations; shaded regions show the 95% Prediction Interval of 1000 simulations; black dashed line shows 14.4 µg/mL target trough concentration; grey dashed line shows mean C_{max} following IV administration of a single dose of CSL346 20 mg/kg to healthy volunteers.

Table 2 Predicted Pharmacokinetic Parameters and Safety Margins

Dose Group	Predicted C_{max} (µg/mL)	C_{max} Safety Margin over Single 20 mg/kg [a]	Predicted $AUC_{0\text{-}28d\_ss}$ [b] (µg•day/mL)	AUC Safety Margin over Single 20 mg/kg [a]
8 mg/kg SC with 3 mg/kg IV loading dose	74	6.3	1336	4.4
16 mg/kg SC with 6 mg/kg IV loading dose	149	3.2	2720	2.1

AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; IV = intravenous; SC = subcutaneous.

[a] In Study CSL346_1001, C_{max} = 472 µg/mL and $AUC_{0\text{-}\infty}$ = AUC from time 0 to infinity, 5839 µg•day/mL after a single 20 mg/kg dose.

[b] $AUC_{0\text{-}28d\_ss}$ = AUC between doses at steady state where dosing interval (τ) = 28 days (4 weeks).

In general, given the absence of safety findings and PD biomarker data from Study CSL346_1001 in healthy volunteers, along with the absence of toxicological findings, selection of doses based on PK / PD data available from murine disease models is the most appropriate. The selected doses of 8 mg/kg and 16 mg/kg SC given every 4 weeks are predicted to maintain subjects at exposures adequate to observe activity and in a range that has been shown to be safe in previous human and nonclinical experience.

3.4 Planned Study Duration

The duration of the study for an individual subject is expected to be up to approximately 34 weeks. This estimate is based on the following:

- An up to 6-week Screening Period
- An up to 4-week Lead-in Period
- A 12-week Treatment Period
- A 12-week Follow-up Period

The overall study duration (ie, first subject's Screening Visit to last subject's EOS Visit) will be approximately 22 months.

3.5 Planned Number of Subjects

The study will randomize a target of 100 subjects:

- 25 subjects randomized to the 8 mg/kg CSL346 group
- 25 subjects randomized to the 16 mg/kg CSL346 group

- 50 subjects randomized to the placebo group

A subject is considered enrolled in the study once they have signed the ICF. A subject is considered eligible for randomization into the study when all inclusion criteria have been met, none of the exclusion criteria have been met, and the randomization criteria have been met (Section 4.1).

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).

3.6 Study Oversight

3.6.1 Independent Data Monitoring Committee(s)

This study will use an IDMC. Voting members of the IDMC will not be employees of CSL Behring (CSL) and will not have a financial interest in the successful development of CSL346. The IDMC will include 3 physicians with expertise in treatment of renal (2) and cardiac (1) disease who are experienced in the conduct and oversight of clinical trials in this space, and a statistician with similar relevant expertise. The IDMC will have appropriate access to unblinded study data to facilitate periodic assessment of the safety of the IP. They will serve as an advisory body and will make recommendations to the Steering Committee (Section 3.6.2) and Sponsor's Study Team regarding continuation, modification, or discontinuation of the ongoing study.

Appropriate background information and ongoing consultation, as well as technical and logistical support, will be provided by CSL. The IDMC will have the ability to request additional external input as needed.

Additional support will be provided by the Sponsor's study Lead Physician, Medical Monitor, Drug Safety Physician, Statistician, Operations Lead, Clinical Scientist, and others, as needed, who will not have access to unblinded study data. Unblinded data and programming support will be provided by appropriate individuals not involved in the conduct of the study and placed under strict confidentiality.

Specific details, including the scope, composition, operating procedures, and meeting frequency, will be documented in the IDMC Charter and ratified by the IDMC before study initiation.

3.6.2 Steering Committee

The Steering Committee, consisting of selected collaborating Investigators, will only have access to blinded study data and will be responsible for the following activities:

1. Providing guidance to the Sponsor with respect to study design, site selection and final data analysis, and publication
2. Providing oversight of study conduct including, but not limited to, the following:
   - Monitoring adherence to protocol – compliance, retention, and protocol violations
   - Independent blinded assessment of AESIs (Section 9.6.2); guidance on management of AESIs, and administration or discontinuation of IP in consultation with the Sponsor Medical Monitor and the Investigator

Steering Committee operation details (eg, scope, composition, operating procedures, and meeting frequency) will be documented in the Steering Committee Charter and ratified by the Steering Committee before study initiation.

3.7 Stopping Criteria

3.7.1 Study Stopping Criteria

The ongoing monitoring of all treatment-emergent AEs including serious adverse events (SAEs) and AESIs as defined in the protocol is performed by the IDMC. The IDMC (unblinded) will use the following stopping criteria to guide recommendations to continue, modify, or discontinue the study:

1. One or more subjects who receive CSL346 develop a treatment-emergent SAE attributed to CSL346 that is life-threatening or results in death
2. Two or more subjects (at least one of which is randomized to the 8 mg/kg dose level) experience any treatment-emergent AESI requiring permanent discontinuation of study treatment ("severe") that are attributed to CSL346 including:
   - Any treatment-emergent AESI requiring permanent discontinuation of study treatment ("severe"), including increases in SCr, ACR, or BP, attributable to CSL346, OR
   - Evidence of cardiac toxicity (SAE or meeting troponin-I stopping criteria; see Section 9.1.3.5) OR
   - A severe injection site reaction

3. One or more subjects experience a treatment-emergent SAE of acute hepatic injury that is attributed to CSL346 and meets the definition of Hy's law:
   - Elevation in alanine transaminase > 3x the upper limit of normal (ULN) and
   - A concomitant elevation in total bilirubin > 2x ULN and
   - Absence of other causes such as viral hepatitis, bile duct disease, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury
4. Two or more subjects experience a treatment-emergent SAE of drug hypersensitivity reaction

Criteria for stopping IP dosing related to AESIs are described in Section 9.1.3.

3.7.2 Dose Level Stopping Criteria

The IDMC (unblinded) may recommend discontinuing the 16 mg/kg CSL346 dose level if 2 or more subjects administered 16 mg/kg CSL346 have any treatment-emergent AESI requiring permanent discontinuation of study treatment ("severe"), that are attributed to CSL346 including the following:

1. Increases in SCr, ACR, or BP
2. Evidence of cardiac toxicity (SAE or meeting troponin-I stopping criteria; see Section 9.1.3.5)
3. A severe injection site reaction

If randomization to the 16 mg/kg CSL346 dose level is discontinued, randomization of subjects will be limited to the 8 mg/kg CSL346 dose level or placebo. The IDMC will provide guidance for ongoing subjects in the 16 mg/kg CSL346 treatment arm.

4 Selection and Withdrawal of Subjects

4.1 Eligibility Criteria

The study population will be selected based on inclusion and exclusion criteria described below. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the Investigator's study team before subjects are included in the study.

4.1.1 Inclusion Criteria

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

1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements.
2. Male and female subjects ≥ 25 years of age at the time of signing the ICF.
3. Current diagnosis of T2DM.
4. Urinary ACR ≥ 150 mg/g (16.95 mg/mmol) from a 24-hour timed urine collection.
5. Renal function: eGFR ≥ 60 mL/min/1.73m^2 based on central laboratory assessment using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
   - With approval of the IDMC, following review of safety and PK data from the first 18 subjects with preserved renal function, subjects with eGFR ≥ 45 mL/min/1.73m^2 can be enrolled.
   - Subsequently, after an IDMC review of safety and PK data from the first 36 subjects (at least 8 with eGFR ≥ 45 to < 60 mL/min/1.73m^2) followed for at least 4 weeks, inclusion of subjects with eGFR > 20 to < 45 mL/min/1.73m^2 will be permitted if approved by the IDMC.

     If inclusion of subjects with eGFR below 60 mL/min/1.73m^2 is endorsed by the IDMC, the following target sample size(s) will be established for subjects with eGFR in the specified range:

     - At least 36 subjects with eGFR < 60 mL/min/1.73m^2
     - At least 18 subjects with eGFR < 45 mL/min/1.73m^2

     To achieve these targeted minimums, a restriction may be imposed on the enrollment of subjects with eGFR ≥ 60 mL/min/1.73m^2 and / or ≥ 45 mL/min/1.73m^2.
6. Glycosylated HbA1c < 12%.
7. Subjects must have been taking stable doses of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) therapy for at least 8 weeks before Screening. Subjects with documented intolerance to treatment with ACEi and ARB can be enrolled.
   - Subjects taking antihypertensive medication(s) must have been taking stable doses for at least 8 weeks before Screening

8. If the subject takes SGLT2 inhibitors, dose must be stable for at least 4 weeks before Screening.
    - Every effort will be made to ensure that at least 50% of randomized subjects are receiving concomitant treatment with an SGLT2 inhibitor
9. Female subjects of childbearing potential (FCBP) and male subjects with a female partner of childbearing potential must agree to use a highly effective form of birth control in addition to a barrier method of contraception (ie, male or female condom with or without spermicide and without fat- or oil-containing lubricants) starting at Screening and through 90 days after last IP administration unless:
    - Male subject has undergone effective surgical sterilization at least 3 months before entering the study
    - The female sexual partner(s) of male subject has undergone effective surgical sterilization at least 3 months before the subject enters the study or is (are) post-menopausal

Acceptable highly effective forms of contraception and the definition of FCBP are described in Section 7.4.

10. Investigator believes that the subject understands the nature, scope and possible consequences of the study.

4.1.2 Exclusion Criteria

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

1. Current diagnosis of type 1 diabetes mellitus.
2. Known medical history or clinical evidence suggesting non-diabetic renal disease, except for concomitant hypertensive nephrosclerosis or a single kidney.
3. History of acute kidney injury (AKI) within 1 year before Screening and change in SCr from Visit 1 to Visit 2 (Day –21) > 0.3 mg/dL (26.5 µmol/L) by central laboratory assessment.
4. History of chronic dialysis or renal transplant; active on a kidney transplant waiting list (awaiting transplant) with a living donor identified, or anticipated transplant within 6 months following randomization in the study.

5. Requirement for concomitant treatment with any prohibited concomitant medication, as indicated in Section 7.3.
6. Uncontrolled hypertension defined as: SBP > 160 mmHg or DBP > 100 mmHg. See also Randomization Criteria (Section 4.1.3).
7. New York Heart Association heart failure Class III or IV within 1 year before Screening.
8. Myocardial infarction, unstable angina, revascularization procedure (eg, stent or bypass graft surgery), cerebrovascular accident, transient ischemic attack, or new clinically important electrocardiogram (ECG) findings within 6 months before Screening, or a revascularization procedure is planned during the study.
9. Left ventricular ejection fraction (LVEF) < 50% by echocardiogram (ECHO).

   An ECHO performed for non-study-related reasons within 3 months before Screening can be used to satisfy this criterion.
10. Troponin-I levels > upper reference limit (URL). See also Randomization Criteria (Section 4.1.3).
11. B-type natriuretic peptide (BNP) > 200 pg/mL.
12. Alanine transaminase > 2x the ULN.
13. Subject is unable to tolerate SC test infusion.
14. Pregnant, breastfeeding, or not willing to cease breastfeeding.
15. History of cancer within 5 years before Screening, with the following exceptions:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin
    - Carcinoma in-situ of the cervix
    - Carcinoma in-situ of the breast
    - Incidental histologic finding of prostate cancer (Stage T1a or T1b using TNM clinical staging)
16. Positive viral test result for hepatitis B virus (HBV) (Appendix 2), hepatitis C virus, or human immunodeficiency virus -1 / -2 at Screening.

17. Any clinically significant abnormalities in clinical chemistry, hematology (including coagulation) or urinalysis results that would make the subject unsuitable to participate in the procedures or intervention of the study, as judged by the Investigator.
18. Participated in another interventional clinical study within 12 weeks before Screening.
19. Previously randomized in the current study.
20. Known or suspected hypersensitivity to CSL346 or to any of its excipients.
21. Any other condition that renders the subject unwilling, unable, or unlikely to comply with the requirements of the study, as judged by the Investigator.
22. Involved in the planning and / or conduct of the study (applies to CSL staff, staff at the study site, and third-party vendors).

4.1.3 Randomization Criteria

To be randomized into the study, subjects must meet the following Randomization Criteria at Visit 3 (Day –7) and Visit 4 (Day 1):

1. SBP ≤ 150 mmHg and DBP ≤ 100 mmHg at Visit 3 (Day –7) and Visit 4 (Day 1). If the subject's BP at Visit 3 (Day –7) or Visit 4 (Day 1) does not satisfy this criterion, randomization / treatment should be delayed and FMV urine samples discarded. The Investigator should ensure the subject is compliant with concomitant antihypertensive medications and can repeat this BP evaluation within 3 to 10 days of the failed criterion. The subject will be instructed to collect 3 additional FMV urine samples.
    - If a subject satisfies the BP criterion at the rescheduled visit, the subject can be randomized.
    - If a subject fails to satisfy the BP criterion at the rescheduled visit, the subject will be considered a Lead-in failure (discontinued from study) and will not be re-screened
    - If a subject fails to satisfy the BP criterion at any 2 visits (including Visit 3, Visit 4, and the rescheduled visit), the subject will also be considered a Lead-in failure (discontinued from study) and will not be re-screened

2. Change in SCr from Visit 2 (Day –21) to Visit 3 (Day –7) ≤ 0.3 mg/dL (26.5 µmol/L) by central lab assessment. Subjects who do not satisfy this criterion may have 1 repeat SCr test performed at an unscheduled visit within 1 week after Visit 3 (Day –7); for these subjects, the randomization criterion will be evaluated based on change in SCr from Visit 3 (Day –7) to the unscheduled visit (≤ 0.3 mg/dL change by central lab assessment). Subjects who qualify must return for randomization (Visit 4 / Day 1) within 1 week after the unscheduled visit. Subjects who do not qualify will be considered a Lead-in failure (discontinued from the study) and will not be re-screened.
3. Troponin-I levels ≤ URL at Visit 3 (Day –7).

4.2 Screen Failures and Re-screening

Screen failures are defined as individuals who consent to participate in the study but who do not meet the eligibility criteria for participation in the study (see Section 4.1). A minimal set of information including demography, eligibility criteria, screen failure details, and any SAE should be recorded on the electronic case report form (eCRF) for all individuals considered screen failures.

Re-screening of screen failure subjects is permitted once after a minimum 2-month interval between screen failure and re-screening (signing informed consent document[s] for the re-screening period). During re-screening, the subject must have all screening procedures and assessments repeated to demonstrate eligibility for the study. All data, including concomitant medications, medical history, and AE data must be updated for documentation of re-screening.

4.3 Discontinuation of Study Treatment and / or Subject Withdrawal

4.3.1 Reasons for Discontinuation of Study Treatment and / or Subject Withdrawal

Subjects may discontinue IP or withdraw from the study at any time at their own request, or at the discretion of the Investigator or CSL for safety, behavioral, or administrative reasons (eg, because of an AE, protocol deviation, loss to follow-up, subject noncompliance, study termination).

In accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) principles of Good Clinical Practice (GCP), the Investigator always has the option to advise a subject to withdraw from the study if the

subject's safety or wellbeing is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

The Investigator should consult with the Medical Monitor before withdrawing subjects or discontinuing IP, then record the reason and date of subject withdrawal or discontinuation of IP in the eCRF and in the subject's medical records.

Refer to Section 4.3.2 for details on handling subject withdrawals.

4.3.2 Procedures for Handling Withdrawals

If a subject is withdrawn from the study, attempts will be made to complete and document Follow-up Visits (Visit 10 and EOS). If the subject is unwilling or unable to return for Follow-up Visits, the site should attempt to collect AE information by telephone at 4 and 12 weeks after the last dose of IP.

If the subject is withdrawn from the study after receiving IP, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the Investigator to complete other study assessments.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, CSL may retain and continue to use any data collected before such withdrawal of consent.

4.3.3 Subjects Lost to Follow-up

If a subject repeatedly fails to return for scheduled visits, the site must make 3 attempts to contact the subject and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and / or should continue in the study. All attempts to contact the subject should be documented in the subject's medical record.

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Subjects lost to follow-up will be considered to have withdrawn from the study.

4.3.4 Replacement Policy

Subjects withdrawn from the study after randomization will not be replaced on an individual subject level. However, 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).

5 Study Interventions

5.1 Investigational Product

5.1.1 CSL346

CSL346 will be manufactured by CSL Limited, Australia in accordance with ICH Good Manufacturing Practice guidelines and local regulatory requirements.

CSL346 is a sterile solution for IV and SC infusion at a concentration of 100 mg/mL in single-use, Type I, 2-mL glass vials. It appears as an opalescent to clear, yellow to colorless liquid with no visible particles.

All doses will be normalized to a standard volume with normal saline to maintain blinding.

Table 3 CSL346 Characteristics

Substance Name	CSL346
Active Substance	Anti-VEGF-B humanized IgG monoclonal antibody
Trade Name	Not applicable
Storage	+2 to +8˚C
Dosage Form	sterile solution for injection containing 100 mg/mL of CSL346 in a 2 mL vial

IgG = immunoglobulin G; VEGF = vascular endothelial growth factor.

5.1.2 Placebo

The placebo comparator is sterile normal saline that is commercially available and will be supplied by the study site.

Table 4 Placebo Characteristics

Substance Name	Not applicable
Substance	Normal saline (0.9% sodium chloride)
Trade Name	Not applicable
Storage	Per manufacturer's instructions
Dosage Form	Sterile solution for injection

5.1.3 Dosing and Administration of CSL346 or Placebo

The Investigator (or delegate) will administer IP at the study site only to subjects included in this study following the procedures set out in this study protocol. Information on the dosing characteristics of IP is provided in Table 5.

Table 5 Investigational Product Dosing

Administration Parameter	CSL346	Placebo
Dose	3 mg/kg IV and 8 mg/kg SC OR 6 mg/kg IV and 16 mg/kg SC	Not applicable
Dose Regimen	Initial loading dose of CSL346 administered IV, followed by SC infusion at least 2 hours but no more than 6 hours later, then every 4 weeks, for a total of 4 SC doses	Matched to CSL346
Mode of Administration	IV; SC	Matched to CSL346
Anatomical Location	IV access in the arm and SC infusion in the abdomen	Matched to CSL346
Total Infusion Volume	All doses will be normalized to a standard volume (10 mL for IV and 20 mL for SC) with normal saline to maintain blinding (calculated based on weight)	Matched to CSL346
Infusion Duration [a]	≥ 20 minutes for IV ≥ 40 minutes for SC [a]	Matched to CSL346

IP = investigational product; IV = intravenous; SC = subcutaneous.

[a] Infusion duration can be adjusted for the second and subsequent SC infusions at the discretion of the Investigator as described in the IMP Handling Manual.

Blinded IP will be prepared and physically blinded by the unblinded pharmacist at the site, and will be delivered to blinded study staff for administration to the subject (Section 6.3.1).

Detailed information on the preparation and administration of IP is provided in the Investigational Medicinal Product (IMP) Handling Manual.

5.1.3.1 Administration and Dose Adjustment

Subjects experiencing a mild injection site reaction deemed unacceptable by the subject or Investigator may have administration and / or dose adjustments (see Section 9.1.3.1).

Detailed information on the preparation and administration of IP with adjusted volumes and doses is provided in the IMP Handling Manual.

5.1.3.2 Treatment Compliance

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.

5.1.3.3 Overdose

Overdose is defined as the infusion or ingestion of any dose (single or cumulative) of IP that is ≥ 10% over the recommended dose. The effects of any potential overdose with CSL346 have not been studied. In case of overdose, the Investigator should contact the Medical Monitor, the subject should be closely monitored, and supportive treatment should be administered, as needed.

See Section 9.6.5 for overdose reporting requirements.

5.1.4 Packaging, Labeling, Supply and Storage

5.1.4.1 Packaging and Labeling

CSL346 will be packaged and labeled by CSL or delegate according to current ICH Good Manufacturing Practice and GCP guidelines and national legal requirements. Specific details regarding packaging of CSL346 are provided in the IMP Handling Manual.

5.1.4.2 Supply and Storage

CSL346 will be supplied to the study sites by CSL or delegate. Placebo is commercially available normal saline and will be supplied by the study site.

At the study site, CSL346 must be stored under temperature-controlled and monitored conditions from +2 to +8˚C in a secure storage area as specified in the IMP Handling Manual.

5.2 Accountability and Destruction

The IP must be used only as directed in the clinical study protocol.

The unblinded pharmacist or delegate will confirm receipt of all shipments of CSL346 in the IRT system.

All supplies of CSL346 must be accounted for throughout the study in the IRT system.

Records for the delivery of CSL346 to the study site, the inventory at the study site, the use by each subject, and the destruction or return of CSL346 to CSL / designee must be maintained by the unblinded pharmacist or delegate using the IRT system.

The Investigator delegate (eg, unblinded pharmacist) must provide reasons for any discrepancies in records of drug accountability.

Any unused vials of CSL346 must not be destroyed until the drug accountability documentation has been checked by the unblinded study monitor, and any necessary permission for destruction has been given by CSL. Any destruction of CSL346 must be documented and certification provided to CSL.

All drug accountability records must be stored in the site file and must be readily available for inspection by the study monitor and / or auditor, and open to regulatory inspection at any time.

Further details regarding accountability and destruction of CSL346 are provided in the site IMP Handling Manual.

5.3 Other Interventions

5.3.1 Concomitant Study-related Therapies

Required concomitant medications are described in the Inclusion Criteria (Section 4.1.1).

Medication / Therapy	Dose	Permitted Period of Use
Stable ACEi or ARB therapy is required unless a subject is intolerant or therapy is contraindicated and reasons are documented	Regimen should be considered appropriate in the judgment of the Investigator	Regimen should be stable for at least 8 weeks before Screening (4 weeks for SGLT2 inhibitors) and remain unchanged throughout the subject's participation in the study
Stable antihyperlipidemia and hypertension regimens[a]		
Other standard of care background medications, including SGLT2 inhibitors		
Stable antidiabetes therapy		Each subject's T2DM should be managed according to standard local guidelines throughout their participation in the study

[a] For subjects being treated for dyslipidemia or hypertension.

5.4 Access to Investigational Product After the End of Study

Subjects will not be provided with IP by CSL after completion or discontinuation from the study.

6 Allocation to Treatment

6.1 Subject Assignment

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

6.2 Randomization Procedures

A randomization scheme will be used to ensure unbiased treatment assignment. Approximately 100 subjects will be randomized to receive 8 mg/kg CSL346, 16 mg/kg CSL346, or placebo in a 1:1:2 ratio via the IRT system. If dose level stopping criteria are triggered (see Section 3.7.2), randomization of subjects will be limited to the 8 mg/kg CSL346 dose level or placebo. The randomization will be stratified by SGLT2 inhibitor use.

Using IRT, limits will be imposed to ensure that at least 50% of the subjects enrolled in the study will be receiving concomitant treatment with an SGLT2 inhibitor. If enrollment of subjects not receiving SGLT2 inhibitors reaches 50% (ie, 50 subjects), further enrollment in the study may be restricted to allow only subjects receiving an SGLT2 inhibitor.

If inclusion of subjects with eGFR below 60 mL/min/1.73m^2 is endorsed by the IDMC, target sample size(s) will be established for subjects with eGFR < 60 mL/min/1.73m^2 and / or eGFR < 45 mL/min/1.73m^2.

To achieve these targeted minimums, restrictions may be imposed on the enrollment of subjects with eGFR ≥ 60 mL/min/1.73m^2 and / or ≥ 45 mL/min/1.73m^2.

Any restriction on enrollment of subjects based on eGFR will be communicated directly to the sites.

To ensure the study blind is maintained, the IRT external service provider will prepare the study randomization code according to the approved randomization specifications. The IRT external service provider will keep the randomization code on file.

6.3 Blinding Procedures

6.3.1 Blinding Method

Unblinded study site personnel delegated by the Investigator (eg, the unblinded pharmacist) will prepare and blind the IP (CSL346 or placebo) in syringes for administration to the subjects.

The unblinded study site personnel will provide the appropriately blinded IP, as assigned by IRT, to the blinded study site personnel ready for infusion. The color of the liquid in the syringe will be obscured by applying a translucent yellow label to the outside of the syringe that renders differences in the color of the contents indistinguishable. The blinded syringe(s) will then be delivered to study staff for administration to the subject. The blinded Investigator (or blinded delegate) will administer the IP.

Study site staff who will be conducting safety assessments, including the Investigator, will be blinded to treatment allocation (ie, whether the subject receives CSL346 or placebo) and to kit number assignment. Subjects and Sponsor staff will also be blinded to treatment allocation (double-blind) and kit number assignment, except as stated below.

A study-independent bioanalyst, pharmacokineticist, statistician, and programming support responsible for the sample analysis, PK evaluation, and IDMC operations will be unblinded as well as a representative from Clinical Trials Supply and from IRT. Additionally, unblinded monitors may be assigned to sites. Designated unblinded personnel agree not to disclose the contents of the randomization schedule, the contents of the kit list, or any subject kit number assignment. The PK and safety-related data provided to the IDMC during the course of the study will be unblinded. All individuals with access to unblinded data will be independent from the study team, and will be placed under strict confidentiality to protect the integrity of the study.

6.3.2 Breaking the Blind for an Emergency

The randomization code for individual subjects may be unblinded to a site during the study in emergency situations for reasons of subject safety, if knowing treatment assignment will change subject management. In case of an emergency situation for the reason of subject safety, the Investigator should use the IRT to identify the treatment allocation for a subject. Whenever possible, the Investigator should consult with the Medical Monitor before unblinding the treatment assignment. The reason for unblinding must be fully documented and the

Investigator must contact the Medical Monitor as soon as possible following any emergency unblinding.

6.3.3 Planned Unblinding Procedures

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 (ie, 4 weeks after the fourth dose). The randomization code will be unblinded once all efficacy data through 16 weeks have been entered into the study database for each subject and these data have been locked. The randomization code will be provided to the statistical vendor group once written authorization of this database lock has been received. These results will be summarized in an interim, nonregulatory, analytical report. 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.

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

6.3.4 Ad-hoc Safety Unblinding

CSL's Global Clinical Safety and Pharmacovigilance personnel may, on an ad-hoc basis, unblind the randomization code directly in the IRT at any time during the study because of a safety concern. The purpose of the unblinded data review is to determine if there is a risk to subject safety that would require further action either for the individual management of a subject or for the ongoing conduct of the study. The need to unblind a subject or group of subjects may not necessarily arise because of an SAE. The need to unblind on an ad-hoc basis will be determined by CSL's Global Clinical Safety and Pharmacovigilance senior leadership.

7 Contraindications, Permitted Therapies and Prohibited Therapies

7.1 Contraindications and Precautions to Further Dosing

No specific contraindications have been established for CSL346. The administration of CSL346 to any subject not meeting the eligibility criteria for this study, or to anyone not enrolled in this study, is prohibited.

7.2 Permitted Therapies

Permitted therapies include any therapy required to treat a condition of the subject that is not prohibited by protocol.

In addition, required concomitant medications are described in the Inclusion Criteria (Section 4.1.1) and in Section 5.3.1.

7.3 Prohibited Therapies

The following therapies are NOT PERMITTED during the study:

Medication / Therapy	Dose	Prohibited Period of Use	Notes
Mineralocorticoid receptor antagonists, combination treatment with RAS inhibitors and ARB, or direct renin inhibitors[a]	NA	Within 8 weeks before Screening through EOS	NA
Trimethoprim, Cimetidine, Cephalosporins, Probenecid, Aminoglycosides, Ketoconazole, Clofibrate, Dronedarone, and Ranolazine.		Within 4 weeks before Screening through EOS	NA
Fenofibrate or nonsteroidal anti-inflammatory agents not taken as part of a stable regimen[a]		Within 8 weeks before Screening through EOS	NA
Immunosuppressive medications, such as cyclosporine, mycophenolate mofetil, tumor necrosis factor-alpha inhibitors, janus kinase inhibitors, or integrin receptor antagonists		Within 8 weeks before Screening through EOS	Systemic corticosteroids are only permitted at low doses for short-term treatment of acute conditions, such as an allergic reaction or gout
Other investigational agents[a]	N/A	Within 12 weeks before Screening through EOS	This is not applicable if the subject is known to have received a placebo as part of another clinical trial

[a] If administration of any prohibited therapy becomes necessary during the study for medical reasons, the subject may be withdrawn from further study treatment and proceed to Follow-up (Section 4.3.2).

7.4 Lifestyle Restrictions

Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must agree to use a highly effective form of birth control in addition to a barrier method of contraception (ie, male or female condom with or without spermicide and without fat- or oil-containing lubricants) starting at Screening and through 90 days after last IP administration.

Childbearing potential is assumed in all female subjects except for the following:

- Female subjects aged > 60 years

- Female subjects aged 45 to 60 years (inclusive) with amenorrhea for ≥ 1 year
- Female subjects who are surgically sterile for at least 3 months before providing informed consent

Highly effective methods of contraception are as follows:

- Abstinence, where abstinence is the preferred and usual lifestyle of the subject, including refraining from heterosexual intercourse during the entire period of risk associated with the IP. Periodic abstinence (calendar, symptothermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea methods are not acceptable definitions of abstinence
- Hormonal methods associated with inhibition of ovulation. Acceptable hormonal methods include oral contraceptives, contraceptive medication patch, contraceptive medication injection, estrogen / progestin vaginal ring, or contraceptive medication implant
- Use of intrauterine device (placed more than 3 months before providing informed consent)
- Bilateral tubal occlusion (3 months before providing informed consent)
- Vasectomy (3 months before providing informed consent)

Additional lifestyle restrictions during the study include the following:

1. Fasting for at least 6 hours before arrival for Visit 3 (Day – 7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16).
2. Restrict alcohol intake to ≤ 7 standard drinks per week and avoid > 2 standard drinks on any single occasion.
3. Subjects should refrain from strenuous physical activity, which is not within the subject's normal daily routine, from 5 days before Visit 3 (Day –7) until after the EOS Visit.
4. Abstain from blood or plasma donation until 3 months after the EOS Visit.
5. Male subjects only: abstain from sperm donation from the first administration of IP until 90 days after the last IP administration.

8 Study Procedures and Visit Schedule

8.1 Clinical Procedures

The timing and frequency of the clinical procedures described in the following sections are detailed in the Schedule of Assessments. All procedures should be performed before IP

administration on dosing days unless otherwise noted. More frequent assessments may be performed, if clinically indicated, at the discretion of the Investigator.

8.1.1 Demographics and Safety Assessments

Subject demographics and safety assessments to be conducted during this study are provided in Table 6. Clinical laboratory assessments are to be performed at time points as detailed in the Schedule of Assessments. The time windows for each type of assessment are detailed in Section 8.6.1.

Table 6 Study Procedures: Demographics and Safety Assessments

Assessment	Description		
Demographics	• Year of birth / age • Sex • Race • Ethnicity (where permitted)		
Medical History	• Relevant medical history within 12 months before Screening • Diagnosis and disease status • Concomitant and prior medications • Contraception method (if relevant)		
Pregnancy Test	• Serum and / or urine tests for beta-hCG		
Virology	• HIV	• HBV (Appendix 2)	• HCV
Physical Examination (full or abbreviated)	• As per the site's standard procedure		
12-lead ECG (triplicate)	• Heart Rate	• PR Interval	• QRS Duration
	• QT Interval	• QTcB Interval	• QTcF Interval
	• Investigator's overall interpretation		
Echocardiogram	• To assess LVEF; Assessed locally as part of subject's eligibility evaluation during Screening. An ECHO performed for non-study-related reasons within 3 months before Screening can be used.		
Troponin-I[a]	• For evaluation of potential cardiac toxicity		
BNP	• To assess signals of potential cardiac toxicity		
Adverse Events	• Evaluation of all adverse events (eg, causality / relatedness, severity, seriousness) • Adverse events of special interest (Section 9.1.3)		
Vital Signs	• Blood pressure (systolic and diastolic)	• Body temperature	
	• Pulse rate		
Height and Weight	• Height at Screening only		
Urinalysis (Screening and Visit 4 / Day 1 only)	• Bilirubin	• Specific gravity	
	• Glucose	• Blood	
	• Nitrites	• Ketones	
	• pH	• Urobilinogen	
	• Leukocyte esterase	• Protein	
Hematology	• Leukocytes (WBC count)		

Assessment	Description		
	• Hemoglobin • Hematocrit		
	• Erythrocytes (RBC count)		
	• Red blood cell indices: MCV, MCH, MCHC, RDW		
	• Platelets		
	• Differential (percentage and absolute): neutrophils, neutrophil band forms, lymphocytes, monocytes, eosinophils, basophils		
	• Reticulocytes		
Coagulation	• INR	• PT	• aPTT
Biochemistry	• Sodium	• AST	
	• Potassium	• LDH	
	• Chloride	• GGT	
	• Bicarbonate	• Bilirubin – total	
	• Carbon dioxide – total	• Direct bilirubin	
	• Calcium	• CRP	
	• Urea nitrogen / BUN	• Cholesterol – total	
	• Creatinine	• Triglycerides	
	• Glucose	• HDL Cholesterol	
	• Protein – total	• LDL Cholesterol	
	• Albumin	• Urate (uric acid)	
	• Alkaline phosphatase	• Creatinine kinase	
	• ALT		
eGFR	• Glomerular filtration rate, estimated using the CKD-EPI equation.		
Immunogenicity[b]	• Analysis for the presence of binding antibodies to CSL346		

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; beta-hCG = beta-human chorionic gonadotropin; BNP = b-type natriuretic peptide; BUN = blood urea nitrogen; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRP = C reactive protein; ECG = electrocardiogram; ECHO = echocardiogram; GGT = gamma-glutamyl transferase; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDL = high density lipoprotein; INR = International Normalized Ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; QTcB = Bazett's correction formula; QTcF = Fridericia's correction formula; RBC = red blood cell; RDW = erythrocyte distribution width; WBC = white blood cell.

[a] A conventional (not high-sensitivity) troponin-I assay specific for the cardiac isoform of troponin-I will be performed by the central laboratory.

[b] Immunogenicity will be assessed via a tiered approach using screening, specificity, and titration assays.

Laboratory Parameters

Details related to the collection, preparation, and transfer of blood and urine samples for laboratory assessments will be provided in the laboratory manual. Tests resulting in abnormal central laboratory values during the study period that have been classified by the Investigator as clinically significant should be repeated by the central laboratory as soon as possible after receiving the laboratory report to rule out laboratory error.

Refer to Section 9.6.2 for assessment of other abnormal laboratory values.

Vital Signs

Vital signs include BP (systolic and diastolic), body temperature, and pulse rate. 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.

Subjects must be seated for at least 5 minutes before vital sign measurements are taken. Instructions for measuring BP will be provided in the Manual of Operations. At Visit 4 (Day 1), measurements will be taken predose, 30, 60, and 120 minutes after the first IV dose of IP but before the first SC dose of IP is administered, then 30 and 60 minutes after SC dosing. Additional measurements will be taken at Visit 2, at Visit 5 (Day 8, approximate T_{max}), at Visit 6, before each subsequent SC IP administration (at Visits 7, 8, and 9), and during Follow-up (at Visit 10 and EOS). Analysis will be based on the mean of 3 measurements at each timepoint.

8.1.2 Pharmacokinetic, and Pharmacodynamic and Exploratory Biomarker Assessments

Pharmacokinetic assessments to be conducted during the study are provided in Table 7. Pharmacodynamic and exploratory biomarker assessments to be conducted during the study are provided in Table 8. Pharmacokinetic time points (relative to IV dose) and windows are provided in Table 10. The time windows for each type of assessment are detailed in Section 8.6.1.

Table 7 Clinical Procedures: Pharmacokinetic Assessments

Procedure	Description
CSL346 (PK Blood Sampling)	Serial blood samples for the determination of CSL346 concentration will be collected at Visit 4 (Day 1). Single PK samples will also be collected at all subsequent visits (before treatment on SC dosing days).
CSL346 (Timed 24-hour Urine)	Urine samples for the determination of CSL346 concentration will be collected at Screening (Visit 1, Baseline), Visit 5 (Week 1), and Visit 9 (Week 12).

PK = pharmacokinetic; SC = subcutaneous.

Table 8 Clinical Procedures: Pharmacodynamic and Exploratory Biomarker Assessments

Procedure	Description
Circulating Biomarkers of Lipid Metabolism	Fasting blood samples for the determination of serum glycerol, NEFA, and ketones will be collected at Visit 3 (Day –7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16). Fasting blood samples for the determination of total cholesterol, triglycerides, HDL, and LDL levels will be collected at Visit 3 (Day –7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16) as part of the standard biochemistry panel.
Circulating Biomarkers of Glycemic Control	Blood samples for the determination of HbA1c levels will be collected at Screening (Visit 1), Visit 4 (Day 1), Visit 10 (Week 16), and EOS. Blood samples for the determination of fasting glucose levels will be collected at Visit 3 (Day –7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16) as part of the standard biochemistry panel.
Other Novel Circulating Biomarkers	Fasting blood samples for the determination of serum free VEGF-B levels[a] and sTNFR1 will be collected at Visit 3 (Day –7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16).
Novel Urine Biomarkers	Urine samples for the determination of VEGF-A, soluble VEGF-R1[a], KIM-1, NGAL, clusterin, and MCP-1 will be collected at Visit 3 (Day –7), Visit 4 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 10 (Week 16).

EOS = End of Study; HbA1c = Hemoglobin A1c; HDL = high-density lipoproteins; KIM-1 = kidney injury molecule-1; LDL = low-density lipoproteins; MCP-1 = monocyte chemoattractant protein-1; NGAL = neutrophil gelatinase-associated lipocalin; NEFA = non-esterified fatty acids; sTNFR1 = soluble tumor necrosis factor receptor 1; VEGF = vascular endothelial growth factor.

[a] Dependent on availability of the assays.

8.1.3 Efficacy Assessments

The efficacy of CSL346 will be assessed based on changes in ACR associated with CSL346 treatment. To minimize intrasubject variability, baseline values for these parameters will be based on the geometric mean values from 3 FMV urine collections on 2 separate occasions (ie, 6 total FMV samples) before the first dose of IP. FMV urine samples for the determination of ACR will be collected as indicated in the Schedule of Assessments. On-treatment assessments of ACR will be the geometric mean values from multiple FMV collections at each time point. Only 2 FMV samples will be collected at Visit 9 because a timed 24-hour sample will also be collected at this Visit. The Follow-up assessment of ACR performed for the primary analysis 4 weeks after the last dose of IP (Visit 10) will be based on the geometric mean of 3 FMV samples. For the EOS Visit, the assessment of ACR will also be based on the geometric mean of 3 FMV samples.

8.2 Other Assessments

8.2.1 Subcutaneous Test Infusion

To ensure that subjects are fully informed about the requirements of the study before enrollment, a 20 mL SC test infusion of normal saline will be administered at Visit 2. This test will be performed after confirmation that assessment results from Visit 1 and assessment results available at the time of Visit 2 (ie, excluding the Visit 2 SCr value) fulfill inclusion / exclusion criteria requirements. The subject and Investigator (or delegate) will have the opportunity to evaluate the tolerability of a 20 mL SC infusion to determine if the subject will be able to tolerate SC infusions every 4 weeks over a 12-week period (4 SC doses).

8.2.2 Exploratory Albumin-to-Creatinine Ratio

As an exploratory assessment, the data generated for the primary analysis (Section 8.1.3) will also be used to evaluate changes in clinical characterization of albuminuria: normoalbuminuria, microalbuminuria, or macroalbuminuria.

To do this, each subject's level of urinary ACR will be categorized at Baseline and at Visit 10 (Week 16) as follows:

- macroalbuminuria (ACR > 300 mg/g [> 33.9 mg/mmol])
- microalbuminuria (ACR ≥ 30 and ≤ 300 mg/g [≥ 3.39 and ≤ 33.9 mg/mmol]), or
- normoalbuminuria (ACR < 30 mg/g [< 3.39 mg/mmol])

Transitions between these categories will be described in the study analyses.

8.3 Sample Collection

8.3.1 Blood Samples

During the study, blood will be taken from each subject for viral testing, laboratory safety assessments, PK / PD evaluations, and future research.

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

Refer to the laboratory manual for details about the volume, collection, storage, handling, and processing of blood samples.

8.3.2 Urine Samples

Timed 24-hour urine samples are collected for determination of ACR during Screening and for detection of CSL346 in urine at other indicated time points. The subject should collect all urine over a 24-hour period and record start and stop time of the collection period.

FMV urine samples are collected for determination of ACR after Screening. The subject's complete FMV should be collected on 3 consecutive mornings, with the third collection on the morning of the indicated visit. For Week 12, a FMV sample should be collected on 2 consecutive mornings, followed by a 24-hour timed sample, as indicated in Table 9.

Sample collection containers should be kept refrigerated by the subject until brought to the study site.

Midstream urine samples for PD analyses will be collected during regularly scheduled study visits as indicated in the Schedule of Assessments and in Table 9.

Table 9 Overview of Urine Collections

Visit	Urine Samples Required	Collection Day(s)
Screening (Visit 1)	Timed 24-hour collection	Within 1 week of Visit 1
Screening (Visit 2)	None	--
Week –1 (Day –7 / Visit 3)	FMV x3 Midstream	Day –9, Day –8, Day –7 Day –7 during visit
Day 1 (Visit 4)	FMV x3 Midstream	Day –2, Day –1, Day 1 Day 1 during visit
Day 8 (Visit 5)	Timed 24-hour collection	Morning of Day 7 through morning of Day 8
Week 2 (Day 15 / Visit 6)	FMV x3	Day 13, Day 14, Day 15
Week 4 (Day 29 / Visit 7)	FMV x3 Mid-stream	Day 27, Day 28, Day 29 Day 29 during visit
Week 8 (Day 57 / Visit 8)	FMV x3 Midstream	Day 55, Day 56, Day 57 Day 57 during visit
Week 12 (Day 85 / Visit 9)	FMV x2 Timed 24-hour collection	Day 83, Day 84 Morning of Day 84 through morning of Day 85
Week 16 (Day 113 / Visit 10)	FMV x3 Midstream	Day 111, Day 112, Day 113 Day 113; during visit
Week 24 (Day 169 / EOS)	FMV x3	Day 167, Day 168, Day 169

EOS = End of Study; FMV = first morning void.

8.4 Retention of Samples for Future Research

Plasma, serum, and urine samples will be retained for future research purposes as indicated in the Schedule of Assessments. These samples may be used to enable development and measurement of additional exploratory biomarkers in the future. Samples for future research will be stored at – 80°C by CSL and retained for up to 10 years. These assessments will not be captured in the clinical database, and will be analyzed and reported separately. Future biomarker analyses may include, but is not limited to, transcriptome profile in peripheral whole blood.

Refer to the laboratory manual for further details about the collection, shipment, storage, and destruction of samples for future research.

8.5 Concomitant Therapies

All drug therapies administered to a subject up to 12 weeks before signing the ICF must be documented in the eCRF. All drugs and / or procedures currently being administered to a subject at the time of signing the ICF, and which continue to be taken in addition to CSL346 during the study, are regarded as concomitant therapies and must be documented in the eCRF. Refer to Section 7.2 and Section 7.3, respectively, for permitted and prohibited concomitant therapies.

8.6 Visit Schedule

8.6.1 Assessment Time Windows

Time windows for all visits and assessments are detailed in Table 10.

Table 10 Time Windows for Visits and Assessments

Visit / Procedure	Time Window (Relative to Scheduled Visit / Procedure)
Visit 1 (Up to –6 weeks; Screening)	Not applicable
Visit 2 (Day –21; Screening)	± 7 days
Visit 3 (Day –7; Lead-in)	± 4 days
Visit 4 (Day 1)	Not applicable
Visit 4 Vital signs	± 15 minutes
Visits 5, 6, and 7 (Weeks 1, 2, and 4)	± 3 days
Visits 8 and 9 (Weeks 8 and 12)	± 5 days
Visit 10 (Week 16; Follow-up)	± 7 days
EOS (Week 24; Follow-up)	± 7 days
PK Blood Sampling Time Points	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).

EOS = End of Study; IP = investigational product; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous.

8.6.2 Screening

8.6.2.1 Screening Visit 1 (Visit 1, ≤ 63 days before Day 1)

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

The following procedures will be conducted and documented at Screening Visit 1:

- Obtain written informed consent and register the subject via the IRT
- Confirm and document that the subject conforms with inclusion / exclusion criteria
- Obtain demographic information
- Obtain medical history
- Perform serum pregnancy test (FCBP only)
- Measure vital signs (BP in triplicate)
- Measure height and weight

- Perform 12-lead ECG (triplicate)
- Confirm LVEF based on local ECHO. An ECHO performed for nonstudy-related reasons within 3 months before Screening can be used.
- Collect blood samples for the following:
  - Viral serology
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
  - Coagulation
- Collect urine sample for standard urinalysis
- Collect subject's timed 24-hour urine sample (leading up to the morning of Screening)
- Collect information on AEs since signing the ICF
- Collect information on prior (within the previous 30 days) / concomitant therapies

The procedures for handling Screen Failures are described in Section 4.2.

8.6.2.2 Screening Visit 2 (Visit 2, Day –21)

Screening Visit 2 should be performed within 6 weeks after Screening Visit 1. The following procedures will be conducted and documented at Screening Visit 2:

- Confirm and document that the subject conforms with inclusion / exclusion criteria
- Perform complete physical examination
- Measure BP (triplicate)
- Collect blood sample for SCr only
- Collect information on AEs
- Collect information on concomitant therapies
- Perform SC normal saline test infusion
- Remind subject to collect FMV urine samples for 3 days leading up to the next visit and to arrive after a minimum 6-hour fast

8.6.3 Lead-in (Visit 3, Day –7)

The following procedures will be conducted and documented at the second Lead-in Visit (Visit 3):

- Confirm and document that the subject conforms with randomization criteria for BP, SCr, and troponin
- Perform serum or urine pregnancy test (FCBP only)
- Perform abbreviated physical examination
- Measure vital signs (BP in triplicate)
- Measure weight
- Perform 12-lead ECG (triplicate)
- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
  - Biomarker analysis
- Collect urine samples for the following:
  - FMV (for Days –9, –8, and –7)
  - Morning midstream
- Collect information on AEs
- Collect information on concomitant therapies
- Remind subject to collect FMV urine samples for 3 days leading up to the next visit and to arrive after a minimum 6-hour fast

8.6.4 Treatment

8.6.4.1 Treatment Visit 4 (Day 1)

8.6.4.1.1 Before Administration of IP

Subjects who complete all Screening assessments and who satisfy the randomization criteria will be enrolled into the study and randomized. After randomization, the following procedures are to be conducted and documented at Visit 4 before administration of IP:

- Confirm and document that the subject conforms with randomization criterion for BP
- Perform serum or urine pregnancy test (FCBP only)
- Perform abbreviated physical examination
- Measure vital signs (BP in triplicate)
- Measure weight
- Perform 12-lead ECG (triplicate)
- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
  - HbA1c
  - Immunogenicity
  - Biomarker analysis
- Collect blood sample for PK before dosing
- Collect urine samples for the following:
  - FMV (for Days –2, –1, and 1)
  - Morning midstream
  - Standard urinalysis
- Collect information on AEs
- Collect information on concomitant therapies

8.6.4.1.2 Administration of IP and After

The following additional procedures are to be conducted and documented at Visit 4 as related to administration of IP:

- Randomization and IRT IP assignment
- Administer IV loading dose of IP
- Measure vital signs (BP in triplicate) at 30, 60, and 120 minutes after IV dose
- At least 2 hours (but no more than 6 hours) after IV dose, administer the first SC dose

- Measure vital signs (BP in triplicate) at 30 and 60 minutes after SC dose
- Collect serial PK blood samples according to Table 10
- Collect information on AEs, including local tolerability assessment
- Remind subject to collect a 24-hour timed urine sample beginning on the morning of Day 7 and continuing until the morning of Day 8

8.6.4.2 Treatment Visit 5 (Week 1, Day 8)

The following procedures are to be conducted and documented at Visit 5:

- Perform abbreviated physical examination
- Measure vital signs (BP in triplicate)
- Measure weight
- Perform 12-lead ECG (triplicate)
- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
- Collect trough PK blood sample
- Collect subject's timed 24-hour urine sample (for Day 7 to Day 8)
- Collect information on AEs, including local tolerability assessment
- Collect information on concomitant therapies
- Remind subject to collect FMV urine samples for 3 days leading up to the next visit

8.6.4.3 Treatment Visit 6 (Week 2, Day 15)

The following procedures are to be conducted and documented at Visit 6:

- Perform abbreviated physical examination
- Measure vital signs (BP in triplicate)
- Measure weight
- Perform 12-lead ECG (triplicate)

- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
- Collect PK blood sample
- Collect urine samples for FMV (for Days 13, 14, and 15)
- Collect information on AEs, including local tolerability assessment
- Collect information on concomitant therapies
- Remind subject to collect FMV urine samples for 3 days leading up to the next visit and to arrive after a minimum 6-hour fast

8.6.4.4 Treatment Visit 7 (Week 4, Day 29)

8.6.4.4.1 Before Administration of IP

The following procedures are to be conducted and documented at Visit 7 before administration of IP:

- Perform serum or urine pregnancy test (FCBP only)
- Perform abbreviated physical examination
- Measure vital signs
- Measure weight
- Perform 12-lead ECG (triplicate)
- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
  - Immunogenicity
  - Biomarker analysis
- Collect trough PK blood sample
- Collect urine samples for the following:
  - FMV (for Days 27, 28, and 29)

- Morning midstream

- Collect information on AEs, including local tolerability assessment
- Collect information on concomitant therapies

8.6.4.4.2 Administration of IP and After

The following additional procedures are to be conducted and documented at Visit 7 as related to administration of IP:

- IRT IP assignment
- Administer the second SC dose of IP
- Collect information on AEs, including local tolerability assessment
- Remind subject to collect FMV urine samples for 3 days leading up to the next visit and to arrive after a minimum 6-hour fast

8.6.4.5 Treatment Visit 8 (Week 8, Day 57)

8.6.4.5.1 Before Administration of IP

The following procedures are to be conducted and documented at Visit 8 before administration of IP:

- Perform serum or urine pregnancy test (FCBP only)
- Perform abbreviated physical examination
- Measure vital signs (BP in triplicate)
- Measure weight
- Perform 12-lead ECG (triplicate)
- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
  - Immunogenicity
  - Biomarker analysis
- Collect trough PK blood sample

- Collect urine samples for the following:
  - FMV (for Days 55, 56, and 57)
  - Morning midstream
- Collect information on AEs, including local tolerability assessment
- Collect information on concomitant therapies

8.6.4.5.2 Administration of IP and After

The following additional procedures are to be conducted and documented at Visit 8 as related to administration of IP:

- IRT IP assignment
- Administer the third SC dose of IP
- Collect information on AEs, including local tolerability assessment
- Remind subject to collect FMV samples on Day 83 and Day 84, to collect a 24-hour urine sample beginning on the morning of Day 84 and continuing until the morning of Day 85

8.6.4.6 Treatment Visit 9 (Week 12, Day 85)

8.6.4.6.1 Before Administration of IP

The following procedures are to be conducted and documented at Visit 9 before administration of IP:

- Perform serum or urine pregnancy test (FCBP only)
- Perform abbreviated physical examination
- Measure vital signs (BP in triplicate)
- Measure weight
- Perform 12-lead ECG (triplicate)
- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
  - Biomarker analysis

- Collect trough PK blood sample
- Collect urine samples for the following:
  - FMV (for Days 83 and 84)
  - Timed 24-hour urine sample (for Day 84 to 85)
- Collect information on AEs, including local tolerability assessment
- Collect information on concomitant therapies

8.6.4.6.2 Administration of the IP and After

The following additional procedures are to be conducted and documented at Visit 9 as related to administration of the IP:

- IRT IP assignment
- Administer the fourth SC dose of the IP
- Collect information on AEs, including local tolerability assessment
- Remind subject to collect FMV urine samples for 3 days leading up to the next visit and to arrive after a minimum 6-hour fast

8.6.5 Follow-up

8.6.5.1 Follow-up Visit 10 (Week 16, Day 113)

The following procedures are to be conducted and documented at Visit 10:

- Perform serum or urine pregnancy test (FCBP only)
- Perform abbreviated physical examination
- Measure vital signs (BP in triplicate)
- Measure weight
- Perform 12-lead ECG (triplicate)
- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
  - HbA1c

- Immunogenicity
- Biomarker analysis

- Collect trough PK blood sample
- Collect urine samples for the following:
  - FMV (for Days 111, 112, and 113)
  - Morning midstream
- Collect information on AEs, including local tolerability assessment
- Collect information on concomitant therapies
- Remind subject to collect FMV urine samples for 3 days leading up to the next visit

8.6.5.2 End of Study (Week 24, Day 169)

The following procedures are to be conducted and documented at EOS:

- Perform serum or urine pregnancy test (FCBP only)
- Perform complete physical examination
- Measure vital signs (BP in triplicate)
- Measure weight
- Perform 12-lead ECG (triplicate)
- Collect blood samples for the following:
  - Standard hematology and biochemistry testing
  - Troponin-I and BNP
  - HbA1c
- Collect trough PK blood sample
- Collect urine samples for FMV (for Days 167, 168, and 169)
- Collect information on AEs
- Collect information on concomitant therapies

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

As per the ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

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

Adverse events may include the following:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study
- A clinical event occurring after consent but before IP administration
- Intercurrent illnesses with an onset after administration of IP

Adverse events do not include:

- Events identified at Screening that meet exclusion criteria
- Medical or surgical procedures (the condition that leads to the procedure is the AE)
- Situations where an untoward medical occurrence has not taken place. For example:
    - Planned hospitalizations due to preexisting conditions, which have not worsened
    - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery)
    - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy)

- Overdose of IP or any concomitant therapy that does not result in any adverse signs or symptoms

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

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

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

9.1.2 Serious Adverse Event

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

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion
- **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe

- **Requires in-patient hospitalization or prolongation of existing hospitalization** – CSL considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent 1 of the above outcomes listed as an SAE criterion

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

9.1.3 Adverse Events of Special Interest

Adverse events of special interest are injection site reactions (Section 9.1.3.1), increase in serum creatinine (Section 9.1.3.2), albuminuria (Section 9.1.3.3), or baseline blood pressures (Section 9.1.3.4), and cardiac AEs (Section 9.1.3.5).

The safety monitoring plan and guidance for assessing and managing AESIs were developed based on the available nonclinical and clinical data with CSL346, and the expected baseline renal function in the study population.

Guidance for assessing and managing renal and cardiac risk were developed to allow for careful observation of subjects enrolled in the study for increases in SCr, increases in albuminuria, increases in BP, and changes in cardiac parameters.

When an AE satisfies the criteria for an AESI detailed below, the Investigator will assess the AESI's potential relationship to the IP. The AE/SAE/AESI eCRF is to be completed, providing additional detail about the AESI. If the Investigator assesses the AESI as not related to treatment with the IP, other known or suspected causes of the AESI should be recorded (eg, noncompliance with SOC medications).

All events will be reviewed with the IDMC during regularly scheduled safety review meetings.

The Investigator must report any AESI using the AE/SAE/AESI eCRF. Reporting requirements for AESIs are detailed in Section 9.6.2.

9.1.3.1 Injection Site Reactions

Injection site reactions are an identified risk with the SC administration of CSL346.

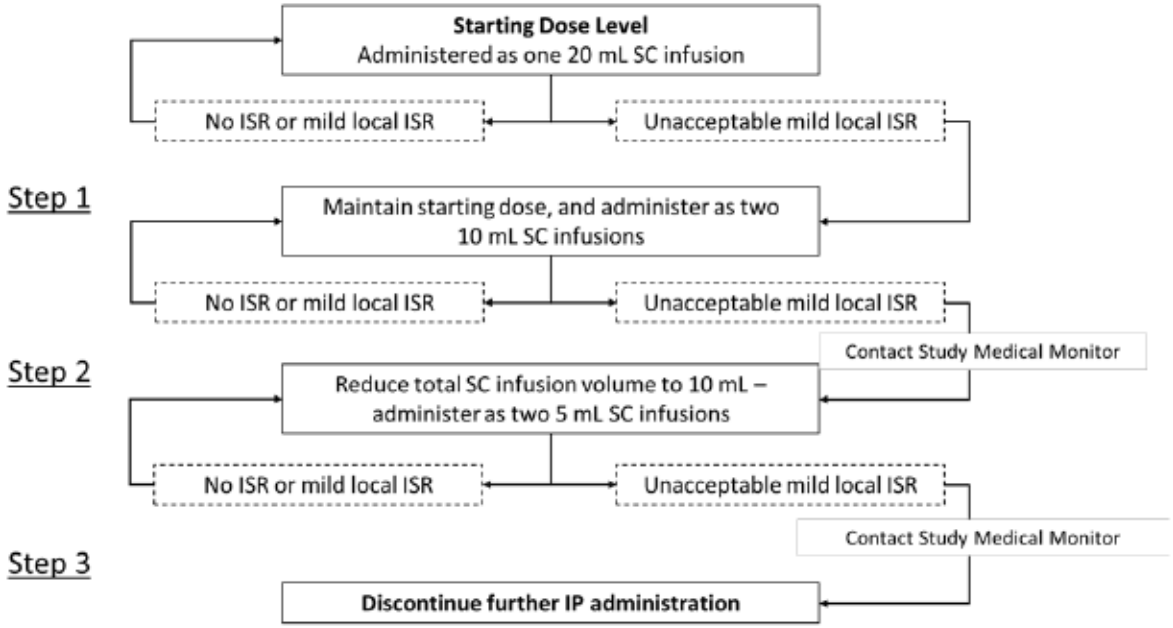
To closely monitor these events, all injection site reactions should be considered AESIs and the AE/SAE/AESI eCRF must be completed.

For mild injection site reactions (defined below) that are deemed unacceptable by the subject or Investigator, and would otherwise lead to discontinuation of the IP, stepwise modification of the volume and / or dose administered should be attempted, as described in Figure 3 and Table 11.

A *mild* injection site reaction is defined as follows:

Tenderness at a site of administration, with or without associated symptoms (eg, warmth, erythema, itching). Mild to moderate pain at a site of administration that resolves within 48 hours.

Figure 3 **Flowchart for Stepwise Modification of Investigational Product Administration Due to Unacceptable Mild Injection Site Reactions**



IP = investigational product; ISR = injection site reaction; SC = subcutaneous.

Note: An unacceptable mild ISR is any event that meets the definition provided that, in the absence of alternative dosing provisions, would result in the subject's discontinuation from further IP administration.

Table 11 **Stepwise Dosing Modification of Investigational Product Administration for Unacceptable Mild Injection Site Reactions**

	Randomized Treatment Arm		
	8 mg/kg Arm	**16 mg/kg Arm**	**Placebo Arm**
Starting Dose			
Dose Level	8 mg/kg	16 mg/kg	Placebo
SC Infusion Volume	20 mL	20 mL	20 mL
Step 1 (≥ Second SC Dose)			
Dose Level	8 mg/kg	16 mg/kg	Placebo
SC Infusion Volume	2 × 10 mL	2 × 10 mL	2 × 10 mL
Step 2 (≥ Third SC Dose)			
Dose Level	8 mg/kg	8 mg/kg	Placebo
SC Infusion Volume	2 × 5 mL	2 × 5 mL	2 × 5 mL
Step 3	Discontinue further dosing		

SC = subcutaneous.

Subjects are randomized into 1 of 3 treatment arms: CSL346 8 mg/kg treatment arm, CSL346 16 mg/kg treatment arm, or placebo treatment arm. At the starting dose, subjects randomized to the 16 mg/kg treatment arm receive a more concentrated dose than subjects in the 8 mg/kg treatment arm because both doses are administered in the same total volume (20 mL). The infusion volume (Figure 3), dose and / or the concentration (Table 11) of IP may be adjusted if there are mild injection site reactions. If a subject has mild injection site reactions at the starting dose that are deemed unacceptable by the subject or Investigator, and would otherwise lead to discontinuation of the IP, proceed to Step 1.

In Step 1, the dose, which is the same as the dose level and concentration of the starting dose, is administered as 2 infusions of 10 mL instead of a single infusion of 20 mL. This adjustment will help determine if reducing the volume infused at a given site reduces the occurrence of injection site reactions. If, after Step 1, the subject continues to have mild injection site reactions that are deemed unacceptable by the subject or Investigator, and would otherwise lead to discontinuation of the IP, contact the Study Medical Monitor to discuss and document the appropriate action to be taken for that subject. If the Medical Monitor approves, proceed to Step 2.

Step 2 is as follows:

- Subjects randomized to the 8 mg/kg treatment arm are to be administered 8 mg/kg CSL346 in two 5 mL SC infusions, halving the total infusion volume and thereby doubling the concentration of CSL346 administered in the previous step
- Subjects randomized to the 16 mg/kg treatment arm are to be administered 8 mg/kg CSL346 in two 5 mL SC infusions, halving the dose level and total infusion volume and thereby maintaining the same concentration of CSL346 administered in the previous step

These adjustments will help determine if reducing the total dose infused at a given site reduces the occurrence of injection site reactions.

If, after Step 2, the subject continues to have mild injection site reactions that are deemed unacceptable by the subject or Investigator, and would otherwise lead to discontinuation of the IP, contact the Study Medical Monitor to discuss and document the appropriate action to be taken for that subject. If the Medical Monitor approves, then move to Step 3 and discontinue further dosing with IP. Every effort should be made to continue the subject's participation in Follow-up Visits even if the IP is discontinued.

For any injection site reaction that exceeds the definition of mild, either in duration or severity of symptoms, the Study Medical Monitor must be contacted to discuss and document the rationale for continuing administration of the IP at a decreased total SC infusion volume and / or dose, or discontinuing further dosing.

9.1.3.2 Serum Creatinine

The criteria for increases in SCr due to AKI are based on a definition of AKI that incorporates absolute changes in SCr over a 24- to 48-hour period (Waikar and Bonventre, 2009). The percent changes in SCr after severe AKI are highly dependent on baseline kidney function. In contrast, the absolute increases in SCr are nearly identical across the spectrum of baseline kidney function. Conservative criteria were identified to trigger a comprehensive evaluation that balances the safety of subjects enrolled in the study with small changes in SCr expected due to intrasubject variability.

An SCr AESI is defined as a confirmed increase from Baseline of at least 0.3 mg/dL. All cases meeting the criteria shown in Table 12 will be specifically reviewed with the IDMC during regularly scheduled safety review meetings.

Table 12 Increases in Serum Creatinine

Serum Creatinine – Increase from Baseline (Confirmed)	Investigator Assessment	Action
≥ 0.3 to < 0.7 mg/dL (≥ 26.5 to < 61.9 µmol/L)	Expected changes due to IP-related activity	Continue IP with increased monitoring
≥ 0.7 mg/dL (≥ 61.9 µmol/L)	Reversible episode of AKI unrelated to IP	Withhold IP until serum creatinine returns to baseline
	IP related	Permanently discontinue IP

AKI = acute kidney injury; IP = investigational product.

If a subject has an increase in SCr that meets criteria outlined in Table 12 at any visit while receiving IP, the Investigator will complete an eCRF reviewing possible causes of AKI not related to IP such as volume depletion, urinary tract infection, and exposure to a nephrotoxic agent. Any identified possible reversible causes of AKI not related to IP will be addressed promptly according to local standards of care. A second measurement will be obtained as soon as possible within a maximum of 1 week. If the specified increase is confirmed, the Investigator will obtain a third SCr value within 1 week and update the eCRF.

The Investigator will contact the Medical Monitor who will assist with evaluation and determination of appropriate action to be taken. This consultation will help discern signs of

possible AKI not related to IP from hemodynamically mediated effects on SCr / eGFR potentially associated with IP-related activity, reversible causes of AKI not related to IP or from renal intrinsic injury related to IP.

The trending changes in SCr over multiple time points will be evaluated in the context of changes in albuminuria, BP, and other clinical parameters over that period, and recommendations will be provided to the Investigator. This may include guidance for heightened monitoring of renal parameters, clinical maneuvers to reverse reversible causes of AKI not related to IP (eg, treat active urinary tract infection), temporary interruption of IP, or permanent discontinuation from IP. The Medical Monitor will be available 24 hours a day and must be consulted by the Investigator; subsequently, the Investigator will make the decision to either administer the next monthly dose of IP or permanently discontinue a subject from treatment. Note that every effort will be made to continue the subject's participation in Follow-up Visits even if IP administration is stopped.

9.1.3.3 Albuminuria

The criteria for increases in albuminuria were derived from an analysis of biological variability in albuminuria levels in subjects with CKD (Waikar et al, 2018). Within subject CV is approximately 30% for FMV urinary ACR and is comparable across the range of baseline values. The high intrasubject variability makes it difficult to distinguish random variability from an adverse effect.

An albuminuria AESI, based on the geometric mean of ACR values from up to 3 FMV samples collected at that on-treatment time point, is a confirmed ≥ 2-fold increase (doubling) from Baseline with additional evidence suggesting AKI. Additional evidence suggesting AKI includes observations such as acute changes in BP or serum creatinine and are described in the study's Manual of Operations.

The following sequence is recommended for evaluation and follow-up:

- Initial flag received from central laboratory for ACR value ≥ 2x baseline value:
    - Site orders urinalysis to be performed locally and urine culture if indicated
    - Obtains 3 additional FMV urine samples for confirmation of increased ACR value by central laboratory
- If confirmed (second ACR flag received from central laboratory):

- Performs novel coronavirus 2019 (COVID-19) polymerase chain reaction test, if indicated
- Repeats hematology (white blood cells and differential, platelet count) and blood chemistry (including blood urea nitrogen analysis at central laboratory
- Obtains vital signs, including body weight and triplicate measurements of BP
- Questions subject about adherence to, or changes in, concomitant medications, and other potential changes to the subject's routine (eg, atypical diet or exercise)

- If additional evidence suggesting AKI is identified, the definition of an albuminuria AESI is met.
  - Completes the AE/SAE/AESI eCRF to indicate an AESI has occurred
  - Updates the AE/SAE/AESI eCRF with any new information (eg, changes in, or missed doses of concomitant medications, AEs)

The Investigator will contact the Medical Monitor who will assist with evaluation and determination of appropriate action to be taken. This may include guidance for heightened monitoring of renal parameters, clinical maneuvers to reverse reversible causes not related to IP, temporary interruption of IP, or permanent discontinuation from study treatment. The Medical Monitor will be available 24 hours a day and must be contacted for consultation before the Investigator decision to either administer the next monthly dose of IP or permanently discontinue a subject from treatment. Note that every effort will be made to continue the subject's participation in Follow-up Visits even if IP is stopped.

All cases meeting these criteria will be specifically reviewed with the IDMC during regularly scheduled safety review meetings.

9.1.3.4 Blood Pressure

An AESI related to BP is 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. In subjects presenting with a SBP ≥ 180 mmHg or a DBP ≥ 120 mmHg, the Investigator will assess the subject for evidence of a hypertensive emergency, treat promptly according to the SOC, and if the subject is confirmed to have a hypertensive emergency, complete an SAE form. Evidence of end organ damage includes hypertensive encephalopathy, retinal hemorrhages, papilledema, or acute and subacute kidney injury. The Investigator should not administer the IP and must contact the Medical Monitor for consultation as soon as

possible and within 1 business day. After consultation with Medical Monitor, the IP may be permanently discontinued or the IP may be resumed with increased monitoring of BP with unscheduled visits as dictated by SOC. Note that every effort will be made to continue the subject's participation in all study visits even if the IP is stopped.

If a subject has an observed SBP ≥ 180 mmHg and / or DBP ≥ 120 mmHg or an increase from Baseline in either SBP or DBP ≥ 20 mmHg and > 160 / 105 mmHg, and the subject has minimal or no symptoms and the increase confirmed at least 30 minutes later, the Investigator should intervene according to SOC as follows:

- If a cause for the rise in BP unrelated to IP administration **is not identified**, the IP may not be administered and the Investigator must contact the Medical Monitor for consultation as soon as possible and within 1 business day. After consultation with the Medical Monitor, the IP may be permanently discontinued or the IP may be resumed with increased monitoring of BP with unscheduled visits as dictated by SOC. Note that every effort will be made to continue the subject's participation in all study visits even if the IP is stopped.
- If a cause for the rise in BP unrelated to IP administration **is identified** (eg, medication noncompliance or other extenuating circumstances), the cause should be addressed and the IP may then be administered. The Investigator should complete an eCRF reviewing possible causes of elevated BP not related to IP. The subject should have unscheduled visits with increased monitoring of BP as dictated by SOC. If the SBP does not return to < 180 mmHg or the DBP does not return to < 120 mmHg, the Investigator must contact the Medical Monitor for consultation before the Investigator makes a decision to either administer the next monthly dose of IP or discontinue a subject from treatment. Administration of IP may continue with increased monitoring of BP as dictated by SOC. Note that every effort will be made to continue the subject's participation in all study visits even if IP is stopped.

All cases will be specifically reviewed with the IDMC during regularly scheduled safety review meetings.

The indicated increases in BP will be measured according to the protocol-specified procedure.

9.1.3.5 Assessment and Management of Cardiac Adverse Events

A cardiac AESI will be defined as any clinically meaningful change from Baseline in cardiac-related parameters, such as ECG intervals, cardiac troponin levels [Thygesen et al, 2018], or LVEF.

If at any point a subject has signs and symptoms consistent with cardiac ischemia, congestive heart failure, or other unstable cardiac event with or without elevated troponin or BNP levels, the subject should immediately be referred to the emergency department for urgent cardiac evaluation. If a cardiac event cannot be ruled out, the subject should permanently discontinue administration of IP and enter the Follow-up Period of the study. The Investigator, or delegate should notify the Sponsor Medical Monitor of the decision to discontinue IP and complete the AE/SAE/AESI eCRF to provide details related to the event.

Cardiac troponin-I (cTnI) will be measured at the central laboratory during Screening and throughout the subject's participation in the study. Subjects with cTnI above the URL for the assay (defined as exceeding the 99th percentile of a normal reference population) during Screening or Lead-in will be excluded from the study.

In the absence of signs and symptoms of an unstable cardiac event, if any cTnI value reported by the central laboratory during Treatment or Follow-up exceeds the URL, the following guidance will be followed:

- Repeat measurement of cTnI within 48 hours to confirm
- Hold next dose of IP until the following steps are completed
- The subject will be referred to the local cardiologist for cardiac evaluation within 1 week, adhering to local standards of care, as indicated. Every effort should be made to seek evaluation by the same cardiologist used to assess LVEF for Screening. As possible, the same methodology should be used for all study-related cardiac assessments
    - If the local cardiologist finds evidence of myocardial damage or unstable cardiac event, such as new wall motion abnormality (WMA) or decreased LVEF to < 50% on myocardial imaging (Echo, radionuclide imaging, or cardiac magnetic resonance imaging scan), new abnormal delayed enhancement on cardiac magnetic resonance imaging, or new Q-waves or ischemic changes on ECG, contact the Study Medical Monitor to determine if IP can be administered, if additional follow-up is needed, or if IP should be permanently discontinued

- If the local cardiologist finds no evidence of myocardial damage or unstable cardiac event, IP administration may resume

Whenever a cardiac-related AE is reported, the site must complete the AE/SAE/AESI eCRF to provide details related to the event.

If a local assessment of cardiac troponin is obtained as part of clinical practice by the site and the value is above the URL for the local assay, the site will perform a clinical assessment based on standard clinical practice. The site will also obtain a central cTnI. If the cTnI is elevated, the above protocol-mandated guidance will be followed.

If any further cTnI value obtained is above the URL, the Sponsor Medical Monitor must be contacted to discuss next steps.

Table 13 Stopping Criteria for Cardiac Troponin-I Levels

Observation	Clinical Care	Action
Asymptomatic: cTnI Increase to > URL (99% Coefficient of Variation)	Refer to local cardiologist for evaluation within 1 week. Implement local standard of care as indicated. Hold next dose until cardiac evaluation and consultation with Study Medical Monitor are complete	If evidence of myocardial damage or unstable cardiac event[a] contact Study Medical Monitor to determine next steps with respect to IP administration. If no evidence of myocardial damage: continue IP Complete eCRF for cardiac AESI
Symptomatic	Refer to emergency department for urgent cardiac evaluation.	If confirmed or suspected cardiac event[a], notify Sponsor Medical Monitor and permanently discontinue IP; begin Follow-up Period; complete eCRF for cardiac AESI.

AESI = adverse events of special interest; cTnI = cardiac troponin-I; ECG = electrocardiogram; eCRF = electronic case report form; IP = investigational product; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; URL = upper reference limit; WMA = wall motion abnormality.

[a] eg, new WMA and / or LVEF < 50% on myocardial imaging (echocardiogram, radionuclide imaging, or MRI), new abnormal delayed enhancement on cardiac MRI, or new Q-waves or ischemic changes on ECG.

9.2 Severity of Adverse Events

The severity of each AE, SAE, and AESI is to be assessed by the Investigator as follows:

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

AE = adverse event.

Source: Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Severity Intensity Scale for Adverse Event Terminology.

9.3 Causality of Adverse Events

The causal relationship of an AE to IP **must always be assessed** by the Investigator. All AEs will be classified as either **related** or **not related** to IP. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered related to IP.

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

- Known pharmacology of CSL346
- Clinically and / or pathophysiologically plausible context
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with CSL346, drug withdrawal or reproduced on rechallenge)

9.4 Observation Period for Adverse Events

The observation period for AE (and SAE or AESI) reporting for an individual subject will start at the time of giving written informed consent for participation in the current study and finish at the individual subject's EOS Visit.

If the Investigator becomes aware of an SAE that has started after the observation period has finished, and there is at least a possible causal relationship to CSL346, the event must be reported to CSL (see Section 9.6.3).

9.5 Follow-up of Adverse Events

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

9.6 Adverse Event Reporting

9.6.1 Adverse Events

At each clinical evaluation, the Investigator (or delegate) will determine whether any AEs have occurred. All AEs are to be recorded in the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs, laboratory findings, and / or symptoms. The Investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the EOS Visit, the AE will continue to be followed up until resolution, stabilization, or the subject is lost to follow-up.

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

9.6.2 Adverse Events of Special Interest

Adverse events of special interest should be reported following expedited reporting procedures, as described for SAEs (Section 9.6.3). All AESIs (including non-serious and serious) that occur during the course of the study, whether or not causally related to IP, must be entered into the AE/SAE/AESI eCRF immediately (within 24 hours of the Investigator becoming aware of the event) and reported to CSL. An assessment of causality to the IP must be included.

9.6.3 Serious Adverse Events

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

For SAEs occurring during the study, the Investigator or delegate will enter all relevant information in the eCRF.

All SAEs that occur during the course of the study, whether or not causally related to IP, must be entered into the eCRF immediately (within 24 hours of the Investigator becoming aware of the event). An assessment of causality to the IP must be included.

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

Any SAE that occurs after the EOS visit that is considered to be causally related to IP must be **reported immediately (ie, within 24 hours of the Investigator becoming aware of the event) to CSL.** Such events are not entered into the eCRF.

The minimum reporting requirements for reporting of SAEs include the following:

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

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

In addition, the Investigator must do the following:

- Report all SAEs to the relevant Institutional Review Board (IRB) / Independent Ethics Committee (IEC) within the timeframe specified by the IRB / IEC
- If the subject is an active participant in the study:
    - Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized
    - Ensure that the causality assessment for all SAEs is entered in the eCRF
- If the subject is no longer participating in the study, report the follow-up information to CSL

In cases of death, the Investigator should supply CSL and the IRB / IEC (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

9.6.4 Other Significant Events

Not applicable.

9.6.5 Overdose

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

Details (ie, volume, location of infusions, infusion rate) of overdose of CSL346 (defined in Section 5.1.3.3) must be recorded in the study treatment administration eCRF. Details of overdose of any concomitant therapy must be recorded in the Concomitant Medication eCRF.

9.6.6 Pregnancy and Breastfeeding

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

If a female subject becomes pregnant or initiates breastfeeding, she must discontinue treatment with the IP immediately, her participation will be discontinued, and the procedure for discontinuation of a subject will be followed, as described in Section 4.3.

CSL must be notified within 5 days of the Investigator becoming aware of the pregnancy (by entry of appropriate data into the eCRF). CSL must also be notified within 5 days of the Investigator becoming aware of any pregnancy occurring at any time up to 3 months after each subject's final study visit.

Whenever possible, a pregnancy in a female subject or female partner of a male subject exposed to CSL346 should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the Investigator to CSL using a Pregnancy Reporting / Outcome Form.

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

9.7 Institutional Review Board / Independent Ethics Committee Reporting Requirements

The time frame within which an IRB / IEC must be notified of deaths and IP-related unexpected SAEs is stipulated by each IRB / IEC. It is the Investigator's responsibility to comply with the requirements for IRB / IEC notification. CSL will provide Investigators with all details of all SAEs reported to health authorities.

10 Statistics

10.1 Sample Size Estimation

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 an 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, ie, ln (1 – 0.27) = –0.315 on the natural log scale, using a 1-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 total sample size 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).

10.2 Description of Study Analysis Sets

10.2.1 Screened Analysis Set

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

10.2.2 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.

10.2.3 Safety Analysis Set

The Safety Analysis Set 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.

10.2.4 Per-protocol Analysis Set

The Per-Protocol (PP) Analysis Set comprises all subjects in the ITT Analysis Set who comply with the protocol and complete treatment. Protocol deviations and treatment discontinuations that will result in exclusion from the PP Analysis Set will be documented in the data review meeting minutes before database lock and before study data unblinding. Protocol deviations and treatment discontinuations may lead to the exclusion of the subject's complete set of data or a portion of the subject's data (eg, excluding efficacy data collected after withdrawal of IP).

10.2.5 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.

10.2.6 Pharmacodynamic Analysis Set

The PD Analysis Set comprises subjects in the Safety Analysis Set for whom analysis results were obtained for at least 1 of the exploratory biomarkers of interest.

10.3 Statistical Analyses and Methods

All analyses will be conducted using SAS Version 9.3 or higher. In general, continuous variables will be summarized using descriptive statistics (number of observations, mean, SD, 95% CI, median, minimum and maximum). For repeated measures, absolute and change from baseline values will be summarized. For parameters which are known to have nonnormal

distributions, natural log transformation may be performed before statistical analysis. Categorical variables will be described using percentages and frequencies.

For randomization, subjects will be stratified according to whether or not their background treatment includes an SGLT2 inhibitor. Every effort will be made to ensure that at least 50% of randomized subjects are currently taking an SGLT2 inhibitor.

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

10.3.1 Subject Disposition and Characteristics

10.3.1.1 Subject Disposition

Summary tables by treatment group (8 mg/kg CSL346, 16 mg/kg CSL346, CSL346 combined, and placebo) and total population will present the following:

- The number of subjects enrolled into the study (ie, signed the ICF)
- The number of subjects randomized and who were withdrawn due to failure to meet the Randomization Criteria
- The number of subjects who received IP
- The number of subjects who prematurely discontinued IP
- The number of subjects who were withdrawn from the study
- The number of subjects who completed the study

Similar tables will also be provided for each strata (ie, the use of concomitant SGLT2 inhibitors).

Reasons for discontinuing the IP and withdrawing a subject from the study will be listed by subject.

10.3.1.2 Subject Characteristics

At minimum, subject characteristics will be presented in summary tables. Continuous data will be summarized by descriptive statistics and categorical data will be summarized by frequency distributions. Age will be described as both a continuous and a discrete variable. Supportive data will be listed by subject.

10.3.2 Efficacy Analyses

Primary Endpoint

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 SGLT2 inhibitors, visit (as a categorical factor), and interactions between visit and each of the other model terms as factors. The primary comparison of interest is a contrast of 0.5 (8 mg/kg CSL346 + 16 mg/kg CSL346) – Placebo. 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). 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). The procedure for determining the covariance model for log ACR residuals will be defined in the SAP. There will be only 1 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.

Two sensitivity analyses will be considered for the primary endpoint. The first such analysis considers the effects of COVID-19 on the primary endpoint. For subjects with treatment discontinuation / interruption due to logistical pandemic-related reasons, 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 contract COVID-19 infection during the study, observations on or after the infection 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 infection date, whichever is earlier. The second sensitivity analysis is a tipping point analysis that will employ multiple imputation for missing data using multiple regression to provide multiple complete data sets. The same MMRM model will be used to analyze the complete data set.

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 (ie, 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, as described in Section 6.3.3. 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.

10.3.3 Safety Analyses

Secondary Endpoints

Treatment-emergent AEs, defined as AEs occurring at or after the start of study treatment, will be summarized for each CSL346 dose level (8 mg/kg and 16 mg/kg) and placebo. An overview summary of AEs, including the number of subjects with any AE; AEs related to study treatment; AEs leading to discontinuation of study treatment; SAEs; and deaths will be produced. Treatment-emergent AEs will be summarized by preferred term and system organ class as well as severity. These analyses will be performed on the Safety Analysis Set. Adverse events of special interest (AESIs) will also be summarized separately.

The analysis of SCr, eGFR, and BP will employ a model similar to the primary endpoint. The analysis for these continuous endpoints is an MMRM analysis of change from Baseline to each postbaseline measurement. Similar to the definition in Section 10.3.2, baseline for these parameters will be the average of the values obtained at Visit 3 and Visit 4 before treatment. The model will include treatment, stratification related to the concomitant use of SGLT2 inhibitors, visit (as a categorical factor), interactions between visit and each of the other model terms, as well as the corresponding baseline measurement as a covariate. As with the primary endpoint analysis, the primary comparison will be of CSL346 (8 mg/kg and 16 mg/kg combined) versus placebo. Exploratory comparisons of CSL346 dose levels with placebo will also be done. These analyses will be performed on the Safety Analysis Set.

10.3.4 Pharmacokinetic Analyses

Secondary Endpoints

Serum concentrations of CSL346 will be listed by individual subject and will be summarized by dose level and nominal time point using descriptive statistics (ie, n, arithmetic mean, SD, CV%, median, geometric mean, geometric CV%, minimum, and maximum). Individual subject CSL346 serum concentration versus time will be plotted on linear and semilogarithmic scales. The C_{trough} of CSL346 will also be summarized visually, by dose level.

PK parameters will be derived using noncompartmental analyses, and will include the following:

- C_{max} after IV loading dose
- T_{max} after IV loading dose
- C_{max} after first SC dose
- T_{max} after first SC dose
- $AUC_{0-\tau}$
- C_{trough} after each dose

The following descriptive statistics will be presented, by dose level, for all PK parameters, except for T_{max}, n, arithmetic mean, SD, CV%, median, geometric mean, geometric CV%, minimum, and maximum. The n, median, minimum, and maximum will be summarized for T_{max}. Additional information on the analyses of PK parameters will be provided in the SAP. These analyses will be performed on the PK Analysis Set.

Dose-adjusted PK exposure parameters will be natural log transformed and analyzed in an analysis of variance model, comparing the 16 mg/kg and 8 mg/kg dose levels. 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. The point estimate and CI will be used to assess dose proportionality.

Exploratory Endpoint

Urine concentration of CSL346 will be listed by individual subject and will be summarized by nominal time point using descriptive statistics. This analysis will be performed on the PK Analysis Set.

10.3.5 Pharmacodynamic Analyses

Exploratory Endpoint

Data from the exploratory biomarkers will be summarized descriptively by treatment and visit for the PD Analysis Set.

10.3.6 Pharmacokinetic / Pharmacodynamic Relationships

Exploratory Endpoint

Pharmacokinetic and PD endpoints will be explored graphically to evaluate potential relationships. These analyses will be performed on the PD Analysis Set. Population PK and PK / PD modelling may be used to further assess time-dependent characterization of PK versus PD endpoints, to be reported separately.

10.3.7 Other Analyses

Secondary Endpoint

The number of subjects with a positive immunogenicity test at any time posttreatment will be counted and compared between treatments with Fisher's Exact Test. The comparison will be of CSL346 (8 mg/kg and 16 mg/kg pooled) versus placebo. This analysis will be performed on the Safety Analysis Set.

Exploratory Endpoints

Exploratory endpoints will employ a model similar to the primary endpoint. The analysis for these continuous endpoints is an MMRM analysis of change from Baseline to each postbaseline measurement. The model will include treatment, stratification related to the concomitant use of SGLT2 inhibitors, 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. Exploratory urinary biomarkers will be normalized to creatinine level for analysis and reporting. Treatment comparisons of interest will be similar to that of the primary endpoint. These analyses will be performed on the PD Analysis Set.

The number of subjects who regress from macroalbuminuria to microalbuminuria or normoalbuminuria, or from microalbuminuria to normoalbuminuria at Week 16 will be counted and compared between treatments using Fisher's Exact Test. The comparison will be of CSL346 (8 mg/kg and 16 mg/kg pooled) versus placebo.

11 Quality Assurance

The study may be subject to an audit by CSL, an authorized representative(s) of CSL and / or inspections by an authorized health authority (eg, US Food and Drug Administration). Health authorities may request access to all study documentation, including source documents for

inspection and copying, in keeping with local regulations. CSL will notify the Investigator of any upcoming audit / inspection.

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

12 Regulatory and Ethics Considerations

12.1 Regulatory Considerations

CSL or its agents will submit the appropriate documents to the local regulatory agencies and will await approval before study start.

This study will be conducted under an US Food and Drug Administration Investigational New Drug application, Therapeutic Goods Administration Clinical Trial Notification, and the Health Research Council of New Zealand and documented in accordance with the applicable regulatory guidelines and requirements.

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

12.2 Institutional Review Board / Independent Ethics Committee

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

12.3 Subject Information and Informed Consent

Informed consent of subjects according to the standards of GCP and the principles in the Declaration of Helsinki must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form and should be deemed appropriate by the IRB / IEC. Subjects, their relatives (or if necessary,

legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

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

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

12.4 Subject Confidentiality

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

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

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

12.5 Indemnity and Compensation

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

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

13 Administrative Considerations

13.1 Clinical Trial Research Agreement

This study will be conducted under a CTRA between CSL ("Sponsor") and the institution(s) representing the investigational study site(s) ("Authority"). Financial support to the investigational site(s) will be detailed in the CTRA. The CTRA must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of the Investigator and CSL, and will form the contractual basis under which the clinical study will be conducted. CTRAs may be executed by electronic signature (current provider DocuSign) in compliance with 21 CFR Part 11 and simple or advanced electronic signature according to EU Regulation No 910/2014 - eIDAS.

13.2 Clinical Study Registration and Results Disclosure

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

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

13.3 Implementation of the Clinical Study Protocol and Amendment(s)

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

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

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

13.4 Protocol Deviations

All instances where the requirements of the clinical study protocol were not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of the Investigator and / or CSL. Clinical study protocol deviations arise when either subjects who have been entered in the study and / or the study sites deviate from the IRB / IEC-approved study protocol.

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

13.5 Documentation and Record Keeping

13.5.1 Data Collection

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

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

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

13.5.2 Data Quality Assurance

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

After completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the Investigator. These data queries must be resolved in a timely manner by the Investigator (or delegate).

13.5.3 Record Retention

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

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

The study may be audited or inspected by qualified delegates from CSL or a competent health authority.

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

13.6 Study and Site Closure

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

13.7 Clinical Study Report

A clinical study report will be written after the completion of the study. CSL or its agent will write the report in consultation with the Investigator or, if applicable, a nominated coordinating

Investigator (or delegate). CSL requires that the coordinating Investigator will sign the clinical study report.

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

13.8 Use of Data and Publications

The rights and obligations of Investigators and CSL concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the CTRA for the study.

14 References

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15 Appendices

Appendix 1 Signatures

Signature on Behalf of Sponsor

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

Protocol Number: CSL346_2001 Amendment 2

I have read the Clinical Study Protocol Amendment 2 titled "A Phase 2a, Double-blind, Randomized, Placebo-controlled, Proof of Concept Study of VEGF-B Blockade with the Monoclonal Antibody CSL346 in Subjects with Diabetic Kidney Disease" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

PPD

Date (DD MMM YYYY)

Signature of Principal Investigator

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

Protocol Number: CSL346_2001 Amendment 2 Site Number

I have read the Clinical Study Protocol Amendment 2 titled "A Phase 2a, Double-blind, Randomized, Placebo-controlled, Proof of Concept Study of VEGF-B Blockade with the Monoclonal Antibody CSL346 in Subjects with Diabetic Kidney Disease".

By signing this Clinical Study Protocol Amendment 2, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the Clinical Study Protocol, the standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and applicable regulatory requirements.

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

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

_____ _____

(Signature) Date (DD MMM YYYY)

_____

(Printed name)

_____

(Title)

Appendix 2 Hepatitis B Testing

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen total (anti-HBc total).

Interpretation of hepatitis B serologic test results is described in Table 14. Subjects are eligible for inclusion in the study if they test:

- Negative for HBsAg, anti-HBc total, and anti-HBs.
- Negative for HBsAg and anti-HBc total, but positive for anti-HBs.
- Negative for HBsAg, but positive for anti-HBc total and anti-HBs.

Subjects are ineligible for inclusion in the study if they test positive for HBsAg, regardless of the results of the other tests.

Subjects who test positive for anti-HBc total and negative for HBsAg and anti-HBs must undergo further testing for the presence of HBV DNA:

- If the subject is negative for HBV DNA, the subject is eligible for inclusion in the study.
- If the subject is positive for HBV DNA or the HBV DNA test is not performed, the subject is ineligible for inclusion in the study.

Subjects who are ineligible for inclusion in the study because of HBV test results should consult a physician with expertise in HBV.

Table 14 Interpretation of Hepatitis B Serologic Test Results

Eligibility	HBsAg	anti-HBs	anti-HBc total
Include	–	–	–
Include	–	+	–
Include	–	+	+
Exclude	+	+ or –	+ or –
Test for HBV DNA[a]	–	–	+

+ = positive; – = negative; anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to HBsAg; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus

[a] Subjects positive for HBV DNA are ineligible and subjects negative for HBV DNA are eligible for inclusion in the study.