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Novartis Research and Development

SEG101/Crizanlizumab

Clinical Trial Protocol CSEG101A2203 / NCT04053764

A Phase II, multicenter, randomized, open label two arm study evaluating the effect of crizanlizumab + standard of care and standard of care alone on renal function in sickle cell disease patients ≥ 16 years with chronic kidney disease due to sickle cell nephropathy (STEADFAST)

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List of abbreviations

Ab	Antibody
ACE	Angiotensin-Converting Enzyme
ACR	Albumin to Creatinine Ratio
ACS	Acute Chest Syndrome
ADA	Anti-Drug Antibody
[redacted]	[redacted]
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	[redacted]
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
APC	Acute Pain Crisis
[redacted]	[redacted]
APTT	Activated Partial Thromboplastin Time
ARB	Angiotensin-Receptor Blocker
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
C5b-9	Complement Membrane Attack Complex
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMO & PS	Chief Medical Office and Patient Safety
[redacted]	[redacted]
COVID-19	Coronavirus Disease Caused by SARS-COV-2 virus
CPO	Country Pharma Organization
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
[redacted]	[redacted]
CV	Coefficient of Variance
DAR	Dosage Administration Record
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
[redacted]	[redacted]
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form

[redacted]

EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme Linked Immunosorbent Essay
EMA	European Medicines Agency
[redacted]	[redacted]
EOS	End of Study
EOT	End of Treatment
ER	Emergency Room
ESA	Erythropoietin-Stimulating Agent
eSAE	Electronic Serious Adverse Event
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyltransferase
HA	Health Authority
Hb	Hemoglobin
HbA	Hemoglobin A
HbA2	Hemoglobin A2
HbC	Hemoglobin C
HbcAb	Hepatitis B Core Antibody
HbF	Fetal Hemoglobin
HbS	Hemoglobin S
HbsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HbSS	Homozygous Hemoglobin S (sickle cell anemia)
HbSβ^0-thal	Hemoglobin S with β-thalassemia
HBV	Hepatitis B Virus
HC	Hydroxycarbamide
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HRQOL	Health Related Quality of Life
HU	Hydroxyurea
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

[redacted]

IFN	Interferon
IG	Immunoglobulin
IgG	Immunoglobulin G
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
IVIG	Intravenous Immune Globulin
KDIGO	Kidney Disease Improving Global Outcomes
KIM-1	Kidney Injury Molecule-1
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LPT	Low Platelet Count
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
mAb	Monoclonal Antibody
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
[redacted]	[redacted]
MCS	Mental Component Summary
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MID	Minimally Important Difference
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
NSAID	Non-Steroidal Anti-Inflammatory Drug
[redacted]	[redacted]
OTC	Over the Counter
PA	Posteroanterior
[redacted]	[redacted]
[redacted]	[redacted]
PCR	Protein to Creatinine Ratio
PCS	Physical Component Summary
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)

[redacted]

PRO	Patient Reported Outcome(s)
PT	Prothrombin Time
PTA	Post-Trial Access
PTX3	Pentraxin-3
QMS	Quality Management System
QTcF	QT Interval Corrected by Fridericia's Formula
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SC5-b9	Soluble complement 5b-9
SCA	Sickle cell anemia
SCD	Sickle Cell Disease
SCN	Sickle Cell Nephropathy
SD	Standard Deviation
[redacted]	[redacted]
SOC	Standard of care
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TNF-α	Tumor necrosis factor alpha
[redacted]	[redacted]
ULN	Upper Limit of Normal
US	United States
VCAM-1	Vascular cell adhesion molecular 1
VOC	Vaso-Occlusive Crisis
VWFag	Von Willebrand factor antigen

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any pre-medication)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient or at a later point in time as defined by the protocol
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained
Investigational drug	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Patient information collected by the investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all crizanlizumab administration is discontinued (if applicable), patients attend an end of treatment visit and follow-up visit, after which no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient
Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study
SelG1	Reprixys humanized anti-P-selectin monoclonal antibody variant
SEG101	Novartis humanized anti-P-selectin monoclonal antibody variant
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient
Study treatment	Any single drug or combination of drugs or intervention administered to the patient as part of the required study procedures. This includes crizanlizumab and standard of care medications
Study treatment discontinuation	When the patient permanently stops taking any of the study treatment(s) prior to the defined study treatment completion date for any reason; may or may not also be the point/time of study discontinuation
Patient Number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of one or more cohorts

[redacted]

Withdrawal of study consent (WoC)/ Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the patient explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

[redacted]

Amendment 3 (02-Dec-2021)

Amendment rationale

The STEADFAST study achieved first patient first visit on 10-Dec-2019. However, there have been ongoing recruitment challenges due to difficulties in identifying the protocol specified patient population and high screen failure rate (57%). Despite various efforts to improve recruitment including two protocol amendments to broaden the eligibility criteria, at the time of this amendment, only 47 out of planned 148 patients were randomized after almost two years. It was assessed that this trial will not complete recruitment within the anticipated timelines. Therefore, a decision has been made to stop recruitment (screening) by November 17, 2021, and all eligible patients are expected to be enrolled by December 15, 2021.

This decision was not triggered by any new and/or unexpected safety concerns. The ongoing patients will continue the study until discontinuation or completion. The primary purpose of this amendment is to adjust the sample size and planned statistical analyses. As a result of the reduced sample size and low statistical power, no formal hypothesis testing will be conducted, and descriptive statistics with the 95% Confidence Intervals will be provided instead.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The main changes made to the protocol are as follows:

- List of abbreviations: List updated.
- Protocol summary: updated sections related to objectives, study design and data analysis according to other updates.
- Table 2-1: Objectives and related endpoints updated to be descriptively evaluated.
- Section 3: Study design updated to reflect the stopping of recruitment and the revised population.
- Figure 3-1: Study design updated according to population changes.
- Table 4-1: Table adjusted as analysis will be descriptive.
- Section 4.1.1: Wording adjusted as analysis will be descriptive.
- Section 5: Population, reduction of the patients enrolled according to the stopping of recruitment.
- Section 6.3.2: Treatment assignment, randomization section was updated to reflect the updated patient number.
- Section 6.5.2: Window for blood samples collection updated.
- [redacted]
- Table 8-3: Laboratory assessments, row related to cytokines/complement and additional tests were updated to clarify timepoint and patient population.
- [redacted]

- [redacted]
- Section 9.2: Study completion and post-study treatment: Updates were provided on access to crizanlizumab for patients randomized to the standard of care alone arm.
- Section 10.1.3: SAE reporting updated as per Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) recommendations.
- Section 12.4.2: Statistical methods adjusted following decision to stop recruitment: hypothesis testing removed as analysis will be descriptive.
- Section 12.4.4: Sensitivity analysis removed, no sensitivity analysis will be done as study will be descriptive.
- Section 12.4.5: Supplementary analyses removed due to the reduction of sample size.
- Section 12.5: Analysis supporting secondary objectives updated to indicate descriptive summary of data.
- Section 12.5.1: Analysis of efficacy endpoints adjusted as analysis will be descriptive.
- [redacted]
- Section 12.8: Sample size calculation adjusted. Added table with precision estimates for sample sizes varying from 20 to 80.
- Table 12-3: Confidence intervals table added.

Summary of previous amendments

Amendment 2 (09-Mar-2021)

Amendment rationale

At the time of this amendment, 23 patients have been enrolled.

The primary purpose of this amendment is to broaden the inclusion/exclusion criteria to allow for greater patient eligibility, modify study assessments, update sample collection requirements to reduce patient burden based on current clinical practice in the management of SCD-related CKD and amend the statistical power and sample size calculation.

Inclusion Criteria #4: Change in eGFR criteria

The eGFR upper limit of 130 mL/min/1.73 m^2 for women was increased to 140 mL/min/1.73 m^2 consistent with the criteria for males as there is no confirmed gender specific correlation with hyperfiltration in SCD patients.

Inclusion Criteria #9: Increase in upper limit for direct bilirubin

The upper limit for direct (conjugated) bilirubin was increased from <2 x ULN to ≤ 3.0 x ULN based on evidence from clinical practice, that SCD patients at baseline may have a higher direct bilirubin and may otherwise meet the inclusion criteria. No hepatic safety concerns have been observed within the crizanlizumab program.

Exclusion Criteria #2: Clarified AKI criteria

[redacted]

Though it can take 3 months for resolution of AKI, it has been noted that a patient's renal function can return to pre-AKI values within 6 weeks. Thus, provision has been added that if the patient's renal function has returned to pre-AKI values with 6 weeks of enrollment the patient can be eligible.

Exclusion Criteria #3: Increase in blood pressure limit

The blood pressure limit was increased from >130/80 to >140/90 mmHg. American Heart Association guidelines define hypertension as ≥130/80 and European Society of Hypertension guidelines define hypertension as ≥ 140/90. It was assessed that changing this upper limit would still be consistent with guidelines and that changing the upper limit would expand patient eligibility without negatively impacting patient safety or the trial objectives.

Exclusion Criteria #5: Renal replacement therapy

Renal replacement therapy encompasses all forms of dialysis and kidney transplantation that might be expected to impact the endpoint, and therefore the exclusion criteria was updated to reflect that patients undergoing renal replacement therapy (i.e. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation) are not eligible for the trial.

Exclusion Criteria # 12: Modified language on prior use of crizanlizumab, monoclonal antibodies and immunoglobulin based agents

Prior use of monoclonal antibody was removed as part of the exclusion criteria due to limited reports of immunogenicity with crizanlizumab. Due to the unknown duration of efficacy of crizanlizumab after the drug is discontinued, any prior use of crizanlizumab is prohibited. Use of immunoglobulin based agents was removed as an exclusion criteria as guidance is given in Section 6.2.1.1 permitted concomitant therapy requiring caution and/or action. Immunoglobulin based agents are to be used with caution.

Exclusion Criteria #14: use of anticoagulants or antiplatelet therapy exclusion removed and concomitant therapy guidance added

Exclusion criteria for therapeutic anticoagulant and antiplatelet usage is removed as current data shows that there is no safety concern for patients receiving anticoagulation/antiplatelet therapy. Section 6.2.1 Concomitant therapy was updated to note that antiplatelet agents or anticoagulants at doses targeting therapeutic levels should be used with caution.

eGFR calculation and use of the Creatinine-based "Bedside Schwartz" equation (2009)

The creatinine-based "Bedside Schwartz" equation (2009) will be used to calculate eGFR for patients under the age of 18 at screening as this is the most accurate calculation of eGFR for adolescents and will reduce the risk of overestimation of eGFR in adolescents. The same formula will continue to be used for the patient throughout the entire trial, independent from patient's age at the time of sample collection.

[redacted]

[redacted]

First morning void sample collection

First morning void sample collection requirement was changed to morning void sample collection to decrease patient burden. Based on current practices, sample collection any time during the morning will allow more flexibility with urine collection and will still adequately control for the variability in ACR values without negatively impacting the robustness of the results. The average of 3 ACR values at screening to determine eligibility and at subsequent timepoints will continue to be used to address the variability in ACR. Similar changes were made for morning voids where PCR is collected.

Laboratory results for patient eligibility

Based on operational challenges with central lab reporting timeframe, local results (with the exception of urine ACR and eGFR which can impact study endpoints) can be used to confirm patient eligibility only in the event that central results are not available within the timeframe required for patient randomization.

Pregnancy Follow-up

The pregnancy follow-up reporting period was updated to reflect pregnancy reporting will occur up to one year after the estimated date of delivery, which is aligned with the Novartis pregnancy follow-up standard requirement. This is consistent with the informed consent.

Clarification of 105-day-follow-up period

The 105-day follow-up period was part of the original study design for both treatment arms to ensure the consistency of assessments as the study team was blinded to the treatment. The intention of the 105-day follow-up period is to capture any potential adverse events including development of anti-drug antibodies after study treatment discontinuation, taking into account the half-life of the drug. Patients who will receive crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up. The end of the safety follow-up period for these patients will be the 30-day follow-up. All other patients are required to complete the 105-day follow-up.

Change to statistical power and sample size

The initial sample size was 170 patients with statistical power of 85%. Due to global impact of the COVID-19 pandemic and long recruitment duration, the feasibility of recruiting 170 patients was reconsidered. It was assessed that 80% power, which results in a reduced sample size of 148 patients total, would be sufficiently robust to satisfy the primary objective of this phase II trial.

Clarification on assessments for patients who discontinue study treatment early

To alleviate patient burden of assessment collection after early study treatment discontinuation, the recommendation that patients should return for all assessments was removed. In order to provide robust data, a mandatory Week 53 urine ACR/PCR visit was added to ensure this data was collected for patients who discontinue study treatment early. The Week 53 urine ACR/PCR

[redacted]

visit should be scheduled 12 months after the first dose of study treatment for patients who early discontinue treatment.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The main changes made to the protocol are as follows:

- Clarification of protocol amendment 1 date to 08-Jul-2020.
- List of Abbreviations, Glossary of terms and Protocol summary updated to reflect changes throughout the document. Updated Section numbers, references and links based on changes.
- Section 1.1.1 Overview of sickle cell disease pathogenesis, Section 3 Study design, Section 5.1 Inclusion criteria (inclusion criteria 4), Section 8.3.3 Estimated glomerular filtration rate, Section 8.3.5 Appropriateness of efficacy assessments and Section 12.5.1 Efficacy endpoints: updated to reflect addition of the Creatinine-based "Bedside Schwartz" equation (2009) for patients <18 and clarify that the CKD-EPI formula should be used for patients ≥ 18.
- Section 1.1.4.1 Crizanlizumab (SEG101): updated to reflect current regulatory approval status of crizanlizumab.
- Section 1.2.1 Study purpose and rationale, Section 3 Study Design, Table 3-1, Section 5 Population, Section 5.1 Inclusion Criteria, Section 12.4.5 Supplementary analysis, and Figure 8-1 Glomerular filtration rate and albuminuria grid to reflect the risk of chronic kidney disease progression: updated eGFR upper limit to 140 mL/min/1.73 m^2 regardless of gender.
- Section 2.1 Primary estimands, Table 12-1 and Section 12.4.3 Handling of intercurrent events of primary estimand: Additional definition of primary estimands added. Additional attribute and intercurrent event added.
- Section 3 Study design, Section 6.2.1 Concomitant therapy, Section 6.5.2 Follow-up for toxicities, Section 8 Visit schedule and assessments, Table 8-1, Table 8-6 Pharmacokinetics and immunogenicity blood collection log, Section 9.1.5 Early study termination by sponsor, Section 9.2 Study completion and post-study treatment, Section 10.1.1 Adverse events, Section 10.1.3 SAE reporting, Section 12.5.2 Safety endpoints: added language that patients who will receive crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up. The end of the safety follow-up period for these patients will be the 30-day follow-up. All other patients are required to complete the 105-day follow-up. Added language to these sections to clarify assessments for patients who will not perform the 105-day follow-up. Removed "EOS" language as end of study will refer to end of trial overall. Clarified study treatment discontinuation language. Updated on-treatment period for safety endpoints based on this update.
- Section 3 Study Design, Section 5 Population, Section 6.3.2 Treatment assignment, randomization, updated to reflect change in sample size from 170 to 148 in Section 12.8.
- Section 3 Study Design: updated language to clarify assessments and time points.

[redacted]

- Section 3 Study Design, Table 8-1 Assessment Schedule, [redacted]
- Section 3 Study Design, Section 8 Visit schedule and assessments, Table 8-1, Section 8.3 Efficacy, Section 8.3.1 Urine albumin to creatinine ratio, Section 8.3.2 Urine protein to creatinine ratio, Section 9.1.1 Study treatment discontinuation, Section 9.2 Study completion and post-study treatment: Removed recommendation that patients who discontinue study treatment early should return for all assessments. These patients will return for a mandatory Week 53 urine ACR/PCR assessment. The Week 53 urine ACR/PCR assessment should occur 12 months after the first dose of study treatment.
- Figure 3-1: updated to reflect change to study design
- Figure 3-1 and Figure 8-1: Updated to reflect that mg/g should be used for ACR assessments.
- Section 4.5 Risks and benefits: Section updated to reflect new information based on latest version of the SEG101 Investigator's Brochure. Section updated to note that no substantial additional risks for patients due to COVID-19 have been identified.
- Section 5.1 Inclusion Criteria: updated inclusion criteria 5 to clarify that ACR will be reported as an average of three screening ACR values for eligibility for consistency with the rest of the protocol.
- Section 5.1 Inclusion Criteria: updated inclusion criteria 6 for consistency with the rest of the protocol as not all patients will be receiving HU/HC.
- Section 5.1 Inclusion Criteria: Inclusion criteria 9 updated direct bilirubin criteria to ≤ 3.0 x ULN.
- Section 5.2 Exclusion Criteria: update exclusion criteria 2 to add more details on exclusionary AKI parameters.
- Section 5.2 Exclusion Criteria: Exclusion criteria 3 updated blood pressure from >130/80 to >140/90 mmHg.
- Section 5.2 Exclusion Criteria: Exclusion criteria 5 updated to include renal replacement therapy as part of the exclusion criteria which covers all forms of dialysis and kidney transplantation that might be expected to impact the endpoint (i.e. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation).
- Section 5.2 Exclusion Criteria: clarified exclusion criteria 12 that patients who have received crizanlizumab and/or other selectin inhibitor prior to the study or plans to receive it during the duration of the study are not eligible for the trial.
- Section 5.2 Exclusion Criteria: removed exclusion criteria 14 "Use of therapeutic anticoagulation or antiplatelet therapy (other than aspirin or non-steroidal anti-inflammatory drugs [NSAIDs]) within the 10 days prior to Week 1 Day 1. Note: Prophylactic anticoagulant dose is permitted, as per local guidelines"

[redacted]

- Section 5.2 Exclusion Criteria: removed exclusion 17 “Received a live vaccine against an infectious disease(s) within 4 weeks prior to Week 1 Day 1” as there is no evidence that this would be a safety concern.
- Section 5.2 Exclusion Criteria: added new exclusion criteria 23. Patients with malignant disease (with exceptions) are not eligible for the trial.
- Section 5.2 Exclusion Criteria: revised exclusion criteria 24 to remove resting QTcF parameter as crizanlizumab has not demonstrated an impact on QT parameters.
- Section 5.2 Exclusion Criteria: added “bilateral” to tubal ligation in exclusion criteria 29 for clarification. Updated exclusion criteria 29 to separate the definition of post-menopausal women and women of no childbearing potential for clarification.
- Section 5.2 Exclusion Criteria: language added to clarify that it is up to the investigator discretion if a patient is included/excluded based on symptoms or positive test for COVID-19. These patients should be managed as per country specific guidelines surrounding COVID-19. Recommendation added that patients who test positive are re-tested prior to initiating study treatment.
- Table 6-3 Criteria for dose interruption: added “temporarily” for clarity on infusion interruption in the case of a Grade 2 IRR.
- Section 6.2.1 Concomitant therapy and Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: updated guidance around antiplatelet and anticoagulant therapy.
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action and Section 9.1.1 Study treatment discontinuation: provided guidance on patients who require renal replacement therapy.
- Section 6.2.2 Prohibited medication: Clarified that use of voxelotor within the last 6 months prior to screening is prohibited to be consistent with the rest of the protocol. Removed immunoglobulin based agent as prohibited medication as it is permitted with caution. Added exclusionary statement that patients previously treated with crizanlizumab are not allowed for consistency with exclusion criteria.
- Section 6.5.1.1 Crizanlizumab: Recommendations added for handling of crizanlizumab administration in case of exposure to COVID-19. Amended CRF name.
- Section 6.5.2 Follow-up for toxicities: Clarified requirement for IRR blood sample collection.
- Section 6.7 Preparation and dispensation: updated guidance on monitoring for potential IRRs.
- Section 6.7.1.1 Handling of study treatment: clarifications added regarding drug accountability and study treatment handling responsibilities.
- Section 7 Informed consent procedures: added additional details about optional genetic consent.
- Section 8 Visit schedule and assessments and Table 8-1 Assessment Schedule: Added visit window to safety follow-up visits to allow for more flexibility. Additional clarifications added for discontinuation of study treatment and withdrawal of consent/opposition to use of data/biological samples.
- Table 8-1: Added separate line and footnote for IRR data collection for clarity.

[redacted]

- Table 8-1: removed “Standard of care” duplicate line.
- [redacted]
- Table 8-1: removed requirement for hematology, clinical chemistry and coagulation panel to be collected at Week 7 Day 1 to reduce amount of blood draws for patients.
- Table 8-1: removed Fetal hemoglobin (HbF) assessment at Week 39 Day 1 to reduce amount of blood draws for patients.
- Table 8-1, Section 8.4.1 Laboratory evaluations, Table 8-3 Laboratory assessments: Added guidance that local platelet sampling should also be performed throughout the trial for adults and adolescents with body weight > 45kg. Patients < 45 kg will not have local platelet samples collected based on current guidance for blood volume collection.
- Table 8-1: Footnote updated to clarify that only if an IRR occurs, blood samples should be collected immediately after the onset of the IRR.
- Section 8.1 Screening: Modified re-screening language based on the impact of COVID-19 and the changes to the inclusion/exclusion criteria across the different versions of the protocol. Added reference to Section 8.4.1.
- Section 8.2 Patient demographics/other baseline characteristics: Rationale for patient demographic data collection added. Added language for concomitant medications and non-drug therapies collection for consistency with the rest of the protocol. Updated to reflect that healthcare resource utilization history including patient disease burden will be assessed. Added collection of coinheritance of alpha thalassemia as part of background medical information.
- Section 8.3.1: updated header from “Albuminuria” to “Urine albumin to creatinine ratio” and clarified that creatinine concentrations will also be measured by the central laboratory.
- Section 8.3.1 Urine albumin to creatinine ratio and Section 8.3.2 Urine protein and creatinine ratio: Additional clarifications and guidance added for urine sample collection
- Section 8.4.1 Laboratory evaluations: removed re-sampling requirement for eligibility lab assessments and added detail that laboratory assessments can be repeated during the screening period. Clarified that local ACR and eGFR results should not be used for eligibility. Removed recommendation for using citrate tubes as there is no evidence from ongoing clinical trials that this reduces platelet clumping for samples analyzed via central laboratory. Added guidance that platelet count should also be assessed by local laboratories.
- Section 8.4.2 Electrocardiogram (ECG): Removed language requiring results being reported on CRF as results will be captured centrally through vendor database. Additional guidance on ECGs collection added.
- Figure 8-2 Timing of study procedures: Figure added.
- [redacted]

[redacted]

[redacted]

- Section 8.5.2.1 Pharmacokinetic and immunogenicity blood collection and handling and Table 8-6 Pharmacokinetics and immunogenicity blood collection logs: removed requirement for PK samples to be drawn prior to immunogenicity sample as order of sample collection is not expected to have impact on analysis.
- Section 8.5.2.2 Analytical method: updated units from µg/mL to ng/mL for consistency with reporting units.

[redacted]

- Section 8.5.5.2 Sickle cell vaso-occlusive crisis event and other acute pain crisis: Added recommendation to follow local guidance/practice for COVID-19 testing if the patient experiences a VOC/other APC and other subtypes of VOC events.
- Section 9.1.1 Title updated from "Study treatment discontinuation and study discontinuation" to "Study treatment discontinuation." New Section 9.1.2 "Discontinuation from study" added for clarity. Section language updated for clarifications on study treatment discontinuation and discontinuation from study.
- Section 9.1.3: Title updated from "Withdrawal of informed consent" to "Withdrawal of informed consent/Opposition to use data/biological samples." Text updated to define withdrawal of consent/opposition to use data/biological samples. Language updated to reflect use of data, including processing of biological samples after withdrawal of consent/opposition.
- Section 9.1.4 Lost to follow-up: language updated to clarify status of patient who is considered lost to follow-up.
- Section 9.2 Study Completion and post-study treatment: clarified post-trial access language as there is no provision of comparator (SoC) after the study.
- Section 10 Safety monitoring and reporting: added language for safety monitoring in the context of a public health emergency in the event on-site study visits are limited or prevented.
- Section 10.1.3 SAE reporting: added language that SAEs should be reported immediately to Novartis to align with Health Authority requirements. Added additional language about SAE collection and reporting for clarity.
- Section 10.1.4 Pregnancy reporting: update language to match ICF that after consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery. Added additional guidance for trial participants who become pregnant for consistency with the rest of the protocol.
- Section 10.3 Protocol exempt adverse events and serious adverse events: added language to note that all details, procedures and hospitalizations related to VOCs will be collected and reported on the eCRF.
- Section 12.3 Treatments: updated to remove "listed"

[redacted]

- Section 12.4 Title updated from "Analysis of the primary endpoint(s)/estimands(s)" to "Analysis supporting primary objectives"
- Section 12.4.3 Title updated from "Handling of missing values/censoring/discontinuations" to "Handling of intercurrent events of primary estimand." Deleted the sentence "The imputation of missing data caused by intercurrent events will be handled by defining the estimand framework" as it is not technically accurate. Not all the intercurrent events will lead to missing data, intercurrent events and missing data are two different concepts.
- Section 12.4.3 Handling of intercurrent events of primary estimand: Included the intercurrent event renal replacement therapy (i.e. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation) as this is newly identified. Handling strategies of this intercurrent event was also added depending on different scenarios, define discontinuation due to renal replacement therapy as non-responders. For the patients who had hemodialysis and continued the treatment with their renal function return to within 10% of their pre-AKI level, the hypothetical strategy will be applied.
- Section 12.4.4 Title changed from "Supportive analysis" to "Sensitivity analysis." Updated the wording "supportive analyses" to "supplementary analyses." Separated sensitivity analysis to align with the primary estimands.
- Added Section 12.4.5 Supplementary analysis: Updated the subgroup analysis on eGFR at baseline based on the inclusion criterion update on eGFR. Deleted the subgroup analysis on chronic NSAID use as there is no clear definition on chronic NSAID use. Updated "Supportive Estimands" to "Supplementary Estimands" as it is more in line with estimands terminology.
- Section 12.5 Title updated from "Analysis of secondary endpoints" to "Analysis supporting secondary objectives"
- Section 12.5.2 Safety endpoints: Clarified that vital signs data and ECG data will be summarized and not listed. Updated language to clarify on-treatment and post-treatment period based on 105-day follow-up change.
- Section 12.5.3 Pharmacokinetics: updated language to clarify descriptive summary statistics will be provide for the crizanlizumab + standard of care treatment arm.
- Section 12.8 Sample size calculation: Reduced power from 85% to 80% resulting in sample size reduction from 170 to 148.
- Section 15 References: updated reference list
- Other administrative and editorial updates for clarity and consistency.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (08-Jul-2020)

Amendment rationale

At the time of this amendment, 1 patient has been enrolled into the study.

The reasons why this amendment was undertaken was to refine the data collection for the assessment of the primary and secondary efficacy endpoints, reduce confounding factors, strengthen the primary estimand framework by providing additional clarity regarding the handling of intercurrent events and clarifying the summary measure, and providing additional clarity on the management of infusion related reactions.

The collection window for urine samples to assess ACR and PCR was shortened due to the stability of urine samples (a clarification from the central laboratory was sent to all sites and a note to file dated 29-Aug-2019 was filed). It is emphasized that patients who discontinue from study treatment early should return for all of the assessments indicated in the Assessment Schedule, including ACR and other efficacy assessments.

The stratification factor was updated from "CKD stage" to "CKD risk category" to include albuminuria, as well as eGFR, in the factor, as albuminuria also affects CKD outcomes. A new figure was added to define the CKD risk categories and, correspondingly, the subgroup analysis based on CKD stage was changed to be based on CKD risk category.

Additional guidance was provided on how to manage infusion-related reactions (IRRs), e.g. with regard to

- use of pre-medication as prophylaxis
- caution in the use of steroids
- slowing/reduction of infusion rate

Blood sample collection was updated based on current data that suggest that administration of crizanlizumab can be associated with IRRs, including pain events, some of which can be severe and/or require hospitalization. In order to better characterize these IRRs, blood samples will be collected pre-dose and post-dose at different time points and analyzed for cytokines, complement analytes and tryptase.

Endari™ in United States of America (L-glutamine: hereafter referred to as HA approved form(s) of L-glutamine) was approved to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years and older in the United States in 2017. It is not known how Endari™ might affect the ACR values. Therefore, Health Authority (HA) approved form(s) of L-glutamine will be allowed only if the patient has been on a stable dose for the full 6 months prior to screening and plans to continue on that dose. Starting any new treatment with HA approved form(s) of L-glutamine during the study is now prohibited. Consistent with this, HA approved form(s) of L-glutamine has been added to the intercurrent event for the initiation or discontinuation of medications. Details to further define all intercurrent events have been added into the protocol with this amendment.

[redacted]

Oxbryta™ (voxelotor: hereafter referred to as voxelotor) was approved by FDA on 25-Nov-2019 for the treatment of sickle cell disease (SCD) in adult and pediatric patients 12 years of age and older. It is also not known how voxelotor might affect the ACR values. Therefore, the use of voxelotor is prohibited during the study and has been added to the intercurrent event estimand framework.

Details of the primary analysis were revised to clarify that the test of the treatment effect will be based on the odds ratio estimated by the logistic regression model, and the null and alternative hypotheses were updated accordingly. It was added that the proportions of patients in each group with at least a 30% decrease in ACR will be presented along with a 95% 2-sided confidence interval for the difference in proportions. Sensitivity analyses of the primary endpoint to provide additional information regarding the treatment effect have been added, as have three new subgroup analyses to ascertain the treatment effect based on Hb, frequency of VOCs at baseline and chronic NSAID use.

As albuminuria affects CKD outcomes, ACR was added into the stratification factor and analysis subgroup, which were revised from CKD stage (based on eGFR) to CKD risk category (based on ACR, as well as eGFR). Similarly, ACR was also incorporated into the definition of CKD progression.

Further review of the secondary endpoints led to clarifications concerning the PCR and PK endpoints.

[redacted]

Other changes were made to facilitate patient recruitment into the study, such as increasing the eGFR upper limit criteria, and adding the provision of a central laboratory for Hb electrophoresis if the country does not have local capabilities. Another such change was a reduction in the dose requirements for SOC medications prior to study entry.

The partial blinding of the Novartis study team was removed due to the following challenges: unavoidable bias due to the fact that most Steering Committee (SC) members are investigators (they could be blinded to the aggregate data; however, they would not be blinded to their patient data), unavoidable bias which could occur by communication with the principal investigators, site staff and monitors who are unblinded and, finally, the necessity of a separate unblinded team to review the data.

Finally, other changes were implemented to align the protocol with the overall crizanlizumab clinical trial program language, including replacement of the current drug or alcohol abuse exclusion criterion with a criterion based on a history of drug or alcohol abuse; changes to the process for the identification of adverse events of special interest; and the collection of data for acute pain crisis managed at home, which are protocol exempt AEs/SAEs.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The main changes made to the protocol are as follows:

[redacted]

Abbreviations: Added abbreviations for fetal hemoglobin (HbF), Health Authority (HA) and multiple imputation (MI), immunoglobulin G (IgG), standard of care (SOC), sickle cell anemia (SCA), antibody (Ab), Kidney Disease Improving Global Outcomes (KDIGO), deoxyribonucleic acid (DNA), high-density lipoprotein (HDL), quality management system (QMS), coronavirus disease caused by SARS-COV-2 virus (COVID-19), low density lipoprotein (LDL), [redacted] hepatitis B surface antibody (HbsAb), hemoglobin A2 (HbA2), hemoglobin C (HbC), hemoglobin A (HbA), posteroanterior (PA), immunoglobulin (IG), acute pain crisis (APC), [redacted], enzyme linked immunosorbent assay (ELISA), [redacted] physical component summary (PCS), mental component summary (MCS), activated partial thromboplastin time (APTT), Country pharma organization (CPO), [redacted] European Medicines Agency (EMA), high performance liquid chromatography (HPLC), mean corpuscular hemoglobin (MCH), minimally important difference (MID), mean corpuscular hemoglobin concentration (MCHC), [redacted] mean corpuscular volume (MCV), electronic serious adverse event (eSAE), intravenous immune globulin and (IVIG) and deleted LOCF and PAS.

- Throughout: For clarity, added "/hydroxycarbamide" or "/HC" wherever hydroxyurea (HU) is mentioned.
- Section 1.1.1: Added text that chronic organ damage due to SCD affects the liver, spleen, and eyes and added a summary from new publication on progression of albuminuria in sickle cell anemia (SCA)
- Section 1.1.2: Clarified that the content of this section relates to treatment for SCN.
- Section 1.1.4.1: Added text regarding the recent approval of crizanlizumab (Adakveo®) by the United States FDA.
- Section 1.1.4.2: Deleted the reference to the Reprixys study code SelG1 as this is explained in the previous section.
- Section 1.2.1: Clarified the grade of albuminuria in patients to be included in the study and updated with Farrell et al reference from ASH-FDA workshop.
- Table 2-1, Section 8.3.5, Section 8.5.1.1 and Section 12.5.1: Consolidated the two PCR endpoints into a single endpoint assessing different categories of PCR improvement and stable and clarified that PCR improvement is defined as a ≥ 20% *decrease* in PCR from baseline.
- Table 2-1: Replaced "PK parameter" in the secondary endpoint with "Crizanlizumab PK measurements" to avoid any confusion that traditional PK parameters will be assessed. Deleted "to evaluate the impact of immunogenicity on exposure (PK)" from the endpoint.

[redacted]

- Table 2-1: Added measurement of vital signs and ECG assessments consistent with full list of secondary endpoints listed in Section 12.5.2
- Section 3, Section 4.1.1, Section 4.3, Section 5.1 and Section 6.1: Clarified that patients included in this study must have been receiving at least one of the standard of care drug listed in the protocol.
- Section 3, Table 4-1, and Section 6.3.2: Updated the stratification factor from CKD stage to CKD risk category to include albuminuria, as well as eGFR, in the factor, as albuminuria also affects CKD outcomes. Added a new figure to define the CKD risk categories. Correspondingly, the subgroup analysis based on CKD stage was changed to be based on CKD risk category (Section 12.4.4).
- Section 3: Added cross references to sections detailing the efficacy assessments.
- Section 4.5: Expanded risk and benefit section to align with IB 10 and included additional information on IRRs.
- Section 4.5: Added language to risk and benefit section regarding the important potential risks of hemorrhages, infections, infusion related reactions and immunogenicity in line with phase III crizanlizumab clinical trial
- Section 4.5: Added language to risk and benefit section regarding lack of evidence on mAb transmission in seminal fluid.
- Section 5.1: Inclusion Criterion 3: Added that Hb electrophoresis to confirm the diagnosis of SCD can be done by a central laboratory if the country does not have local capabilities. Correspondingly, the requirement for local assessment was deleted from Table 8-1.
- Section 5.1: Inclusion Criterion 6: Reduced the stable dose requirements for SOC from at least 6 months to at least 3 months prior to study entry for HU/HC. The dose requirements for ACEI/ARBs were changed to reduce the minimum duration of ACE inhibitor/ARB from 6 months to 3 months prior to study entry. Correspondingly, the stable dose requirements were updated in Section 3, Section 4.1.1, Section 6.1, Section 6.5.1.2, Table 6-1 and Section 8.3.5.
- Section 5.1: Inclusion criterion 4: Increased upper limit of eGFR to ≤ 130 (women), ≤ 140 (men) mg/min/1.73 m^2 based on CKD-EPI formula. Correspondingly, Section 1.2.1, Section 3, Section 5, footnote of Figure 8-1, and Section 12.4.4 have been updated with this data.
- Section 5.1: Inclusion criteria 8: updated for clarity (added “at the time of enrollment”)
- Section 5.1: Inclusion criterion 11 was added: Up-to-date record of immunizations, as per local requirements
- Section 5.2: Exclusion Criterion 3 blood pressure requirements were modified in line with the American Society of Hematology 2019 SCD guidelines.
- Section 5.2: New Exclusion Criterion 4 added to exclude patients with a body mass index of ≥ 35 kg/m^2
- Section 5.2: Exclusion criteria 9: updated for clarity (added “defined as <25 g/L”)
- Section 5.2: Exclusion Criterion 12 was modified to exclude any patients who have current or previous use of crizanlizumab within 12 months of screening. Section 5.2: New Exclusion Criterion 13 added to exclude patients currently on voxelotor or received voxelotor within 6 months of screening.

[redacted]

- Section 5.2: New Exclusion Criterion 15 added to exclude patients using HA approved form(s) of L-glutamine within 6 months prior to screening, unless it has been used at a stable dose for the full 6 months.
- Section 5.2: New Exclusion Criterion 19 added to exclude patients with uncontrolled diabetes.
- Section 5.2: Exclusion Criterion 24 (renumbered to 28), current drug or alcohol abuse, was replaced with a criterion to exclude patients with current drug or alcohol abuse as per investigator discretion. Correspondingly, the drug screen was deleted from Section 6.2.2, Table 8-1, Section 8.4.1, and Table 8-3.
- Section 6.1: Added a new table and text to clarify the standard of care requirements, which have been updated.
- Section 6.1: Clarified that evidence that the patients have been receiving the standard of care medication(s) at a stable dose should be documented in the source documents.
- Section 6.1.5 and Section 9.2: Added that Post-Trial Access (PTA) to crizanlizumab also applies to patients randomized to the standard of care alone arm if the study results show superiority of crizanlizumab + standard of care.
- Section 6.2.1: Clarified that NSAID use should be avoided within 48 hours prior to ACR measurement.
- Section 6.2.1.1: Language added on recommendations for pre-medication.
- Section 6.2.1.1: Added an instruction for investigators to contact the Novartis medical monitor regarding the collection of PK/PD samples before and after transfusions.

  Section 6.2.1.1: Clarified that use of HA approved form(s) of L-glutamine is permitted as long as the dose is stable for 6 months before screening.
- Section 6.2.2: Added voxelotor as prohibited medication.
- Section 6.2.2: Added that starting any new treatment with HA approved form(s) of L-glutamine from within 6 months prior to study entry up to the end of the study is prohibited.
- Section 6.4: Treatment blinding: Changed the language to remove partial blinding of the Novartis study team and deleted the Blinding and unblinding plan (previous table 6-2).
- Section 6.5.1.1 Added recommendation about COVID-19.
- Section 6.5.1.1: Table 6-3 updated regarding management of IRRs.
- Section 6.5.1.2: Amended heading to specify that the standard of care is for SCD-related CKD.
- Section 6.5.2: updated to include follow up of toxicities with addition of measuring cytokines, complement, tryptase and p-selectin.
- Section 8, Section 8.3, Section 8.3.1, and Table 8-1: Added text to emphasize that patients who discontinue study treatment early should not be considered withdrawn from the study unless they withdraw their consent. Where possible, they should return for all of the assessments indicated in Table 8-1, including ACR, and other efficacy assessments.
- Table 8-1 and Section 8.4.1.1: Added an assessment for fetal hemoglobin (HbF) and noted that the baseline HbF data will be recorded (Section 8.2).

- Table 8-1: Added a footnote that other acute pain crises managed at home will also be collected. Correspondingly, the definition of other acute pain crisis managed at home was added (Section 8.5.5.2); Table 8-8 was updated with respect to the collection plan for other acute pain crisis; and other acute pain crisis was added as a protocol exempt AE (see the change for Section 10.3 below).
- Table 8-1: Added a footnote to clarify safety procedures should be done as described on Table 8-2.
- Section 8.3.1 and Section 8.3.2: Shortened the 7-day window for the collection of urine samples to assess albumin to creatinine and protein to creatinine ratios due to the stability of the urine samples. Per the revised schedule, patients will collect two of the three samples as first morning voids the day before and the morning of the applicable visits. The third sample will be taken during the patient's visit.
- Section 8.3.2: Added text to emphasize that patients who discontinue study treatment early should return for all of the assessments indicated in Table 8-1, including PCR.
- Section 8.3.4 and Section 8.3.5: The method to assess CKD progression was updated to include ACR in addition to eGFR and Figure 8-1 was added for clarity.
- Section 8.3.5: Added stable dose requirements for HA approved form(s) of L-glutamine use and provided the reason for these requirements and updated with Farrell et al reference from ASH-FDA workshop.
- Table 8-2: Clarified that blood pressure will be based on an average of 3 measurements to reflect standard clinical practice.
- Table 8-3 : Added RNA testing for viral load for consistency with the exclusion criterion.
- Section 8.4.2, Table 8-4 and Section 12.5.2: Changed local ECG interpretation to interpretation by a central reader to improve standardization of ECG interpretations.
- [redacted]
- Section 8.4.5: clarified that diagnostic evaluation for the AKI event would be based on AKI stages 1, 2 and 3 from KDIGO 2012 guidelines
- Section 8.5.2 and Section 12.5.3: Clarified that crizanlizumab pre-dose/trough PK samples will be collected along with the immunogenicity samples and will be used to evaluate the impact of immunogenicity on exposure (PK).
- Section 8.5.3, Table 8-1, Table 8-3: Added cytokines, complement, tryptase and p-selectin collection.
- [redacted]
- Section 10.1.1: Revised the plan for the identification of AEs of special interest (AESIs). AESIs will not be identified by investigators based on an AESI list included in the eCRF, but will be identified at the analysis stage based on the AESIs included in the most recent version of the electronic case retrieval sheet for crizanlizumab trials available at the time of a database lock for an analysis.
- Section 10.1.1: Added eGFR ranges for CTCAE Grade 1 and 2 AEs of CKD progression.
- Section 10.2.3: Added SCD experts to the list of Steering Committee members.

[redacted]

- Section 10.3: Added that other acute pain crises managed at home will be protocol exempt AEs/SAEs for consistency with the protocol exempt AEs/SAEs implemented in the SEG101 program.
- Section 10.3: Clarified reporting of VOC events.
- Section 12.1: Section 12.1.3 was deleted the PK Analysis Set (PAS), as there will not be a PAS in this study.
- Section 12.4.2 and Section 12.4.3: Updated the details of the primary endpoint analysis to clarify that the test of the treatment effect will be based on the odds ratio estimated by the logistic regression model rather than the proportions of patients with a ≥ 30% decrease in ACR. The null and alternative hypotheses were correspondingly updated to be based on the odds ratio, as was the summary measure in the primary estimand framework. It was added that the proportions of patients in each group with at least a 30% decrease in ACR will be presented along with a 95% 2-sided confidence interval for the difference in proportions.
- Section 12.4.3 and Table 12-1: The primary estimand framework was updated with respect to the target population, addition of HA approved form(s) of L-glutamine and voxelotor into the intercurrent events, and modification of the summary measure to be based on the odds ratio of the treatment effect. Further details were added regarding the handling of intercurrent events.
- Section 12.4.4: Supportive analyses of the primary efficacy endpoint were added to assess the effect of including all patients who discontinued treatment prior to the 12month assessment as non-responders, and the effect of including all observed on study data regardless of the usage of NSAIDs.
- Section 12.4.4: Amended the subgroup analysis of CKD stage to be based on CKD risk at baseline (see the Section 3 change listed above); clarified that the subgroup analyses based on HU/HC use and age will be based on categories at baseline; and specified the race subgroups as this is now possible based on the countries of expected recruitment.
- Section 12.4.4: Added three new subgroup analyses, based on chronic NSAID use, Hb at baseline and the frequency of VOCs at baseline.
- Section 12.5: Added clarifications regarding the secondary endpoints; moved the text summarizing the analysis sets to be used into this section.
- Section 12.5.2: Included cytokines, complement, tryptase and p-selection as part of the laboratory assessments for safety monitoring.
- [redacted]
- Section 12.8: Changed the sample size calculation to be based on a two sample z test (and not a two sample t test).
- Section 15: Added the following additional references: Brandow et al., Farrell et al, Niss et al, Asnani and O'Lynch, Emerson and Lutty, Liem et al, and Saunthararajah and Vichinsky. The same changes were made wherever applicable in the protocol summary.

Additional minor changes such as the correction of typographical errors were also made.

[redacted]

IRBs/IECs

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[redacted]

Protocol summary

Protocol number	CSEG101A2203
Full Title	A Phase II, multicenter, randomized, open label two arm study evaluating the effect of crizanlizumab + standard of care and standard of care alone on renal function in sickle cell disease patients ≥ 16 years with chronic kidney disease due to sickle cell nephropathy (STEADFAST)
Brief title	Study exploring the effect of crizanlizumab on kidney function in patients with chronic kidney disease caused by sickle cell disease
Sponsor and Clinical Phase	Novartis/Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to explore the effect of P-selectin inhibition with crizanlizumab on renal function in sickle cell disease (SCD) patients with chronic kidney disease (CKD) who are receiving standard of care medications for SCD-related CKD, have Grade A2 to A3 albuminuria and Stage 1-3a CKD, and who are at higher risk of rapid decline in their estimated glomerular filtration rate. The presence of P-selectin expression in the kidneys has been established based on in vitro and in vivo data, and there is evidence that P-selectin is upregulated in the kidney in response to renal ischemia-reperfusion injury in SCD. Expression of P-selectin in a glomerulonephritis induced mouse model was associated with rapid accumulation of neutrophils in glomeruli and significant proteinuria. P-selectin inhibition in this model was shown to abrogate glomerular neutrophil accumulation and prevented development of proteinuria. It is assumed that administration of crizanlizumab, a P-selectin inhibitor, might have a beneficial effect in SCD patients with CKD by blocking P-selectin mediated multicellular adhesion (including leukocytes), and proteinuria, and also reducing vaso-occlusion and potentially its downstream effects in the renal vasculature, which can be clinically demonstrated by a decrease in proteinuria and slowing the decline in glomerular filtration rate (GFR).
Primary Objective	The primary objective of this study is to evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on albuminuria (ACR) decrease at 12 months, as assessed by the proportion of patients with ≥ 30% decrease in ACR at 12 months from baseline. The primary clinical question of interest is: What is the effect of crizanlizumab + standard of care and standard of care alone on renal function in SCD patients with SCD-related CKD.

[redacted]

Secondary Objectives	• To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on change in albuminuria (ACR), as assessed by the mean change in ACR from baseline to 3, 6, 9, and 12 months of treatment • To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on albuminuria (ACR) decrease at 6 months, as assessed by the proportion of patients with ≥ 30% decrease in ACR at 6 months from baseline • To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on protein to creatinine ratio (PCR) at 12 months, as assessed by the proportion of patients with PCR improvement and stable PCR (improvement: ≥ 20% decrease in PCR from baseline; stable: within ± 20% change from baseline) at 12 months from baseline • To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on the percentage change in eGFR, as assessed by the percentage change in eGFR from baseline to 3, 6, 9, and 12 months of treatment • To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on ACR decline rate, as assessed by the slope of ACR decline from baseline to 12 months of treatment based on ACR values at baseline and at 3, 6, 9, and 12 months • To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on eGFR decline rate, as assessed by the slope of eGFR decline from baseline to 12 months of treatment based on eGFR values at baseline and at 3, 6, 9, and 12 months • To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on the progression of CKD at 12 months, as assessed by the proportion of patients with progression of CKD from baseline to 12 months • To evaluate descriptively overall safety and, tolerability of crizanlizumab + standard of care and standard of care alone, as assessed by the frequency and severity of adverse events (AEs), deaths, measurement of vital signs, ECG assessments, serious AEs (SAEs), and laboratory abnormalities • To assess descriptively the immunogenicity of crizanlizumab over the study period (treatment of 1 year + 105 days of follow-up), as assessed by measurement of anti-drug antibodies to crizanlizumab at select time points; crizanlizumab pharmacokinetic (PK) measurements will accompany immunogenicity measurements • To evaluate descriptively healthcare resource utilization (visits to emergency room (ER) and hospitalizations) in crizanlizumab + standard of care arm and standard of care alone, as assessed by the annualized rate of visits to ER and hospitalizations due to acute kidney injury (AKI) events, vaso-occlusive crises (VOCs), or other SCD complications
Study design	This is a multicenter, randomized two arm, open label study to evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on renal function in SCD patients with SCD-related CKD. Approximately 50 patients will be randomized 1:1 to receive either crizanlizumab (5 mg/kg) + standard of care or standard of care alone. Patients will be stratified at randomization based on CKD risk category (moderate risk or high/very high risk) and HU/HC prescription (Yes/No). The CKD risk

	categories used for stratification are based on both eGFR and albuminuria assessed by ACR.
Population	This study will include patients aged ≥ 16 years with SCD-related CKD. Homozygous hemoglobin (Hb) S (sickle cell anemia) (HbSS) and Hb S (HbS) with β-thalassemia (HbSβ^0-thal) SCD genotypes are eligible. Eligible patients will have an eGFR of ≥ 45 to ≤ 140 mL/min/1.73 m^2 and an ACR of ≥ 100 to < 2000 mg/g; based on previous studies, this population of patients will likely include patients at risk for rapid eGFR decline.
Key Inclusion criteria	• Male and female patients ≥ 16 years on the day that signed informed consent is obtained • Confirmed diagnosis of SCD by hemoglobin (Hb) electrophoresis by a central laboratory if the country does not have local capabilities) or high performance liquid chromatography (performed locally). HbSS and HbSβ^0-thal SCD genotypes are eligible • Patients with eGFR ≥ 45 to ≤ 140mL/min/1.73 m^2 based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (patients ≥ 18) or the Creatinine-based "Bedside Schwartz" equation (patients < 18) • Patients with ACR of ≥ 100 to < 2000 mg/g (taken as an average of the three screening ACR values to determine eligibility). • Receiving at least 1 standard of care drug(s) for SCD-related CKD according to local guidelines. If receiving HU/HC, the patient must have been receiving HU/HC for at least 6 months and on a stable dose for 3 months prior to study entry. If receiving an ACE inhibitor and/or ARB the patient must have been receiving the drug for 3 months and also on a stable dose for those 3 months prior to study entry, in all cases, patients must plan to continue taking the drug(s) at the same dose and schedule until the patient has reached the end of the study. • Hb ≥ 4.0 g/dL, absolute neutrophil count ≥ 1.0 x 10^9/L, and platelet count ≥ 75 x 10^9/L • Patients who are clinically stable and are in a non-crisis state at the time of enrollment
Key Exclusion criteria	• History of stem cell transplant • Patients with evidence of AKI within 3 months of study entry (can decrease interval to within 6 weeks of study entry only if renal function has returned to pre-AKI values prior to study entry) • Blood pressure > 140/90 mmHg despite treatment • Patients undergoing renal replacement therapy (i.e. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation) • Received blood products within 30 days of Week 1 Day 1 • Participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes). Transfusions for acute complications are permitted (acute chest syndrome, acute splenic sequestration, acute hepatic sequestration, worsened anemia) • History of kidney transplant • Patients with hypoalbuminemia defined as <25 g/L • Patient has received crizanlizumab and/or other selectin inhibitor or plans to receive it during the duration of the study. Use of HA approved form(s)

	of L-glutamine within 6 months of screening, unless it has been used at a stable dose for the full 6 months • Currently on voxelotor or received voxelotor within 6 months of screening • Patients with active human immunodeficiency virus, Hepatitis B and Hepatitis C infection • Evidence of CKD attributed to causes other than SCN • Evidence of current drug or alcohol abuse per investigator discretion
Study treatment	Patients will be randomly assigned to one of the following treatment arms in a ratio of 1:1: • Crizanlizumab + standard of care • Standard of care alone Patients with SCD-related CKD will likely be receiving at least one of the following medications – HU/HC, ACE inhibitors, and/or ARBs, as established prior to study entry, and this will be considered their standard of care (patients included in this study must have been receiving at least one of these drugs). The efficacy of crizanlizumab added to standard of care and standard of care alone will be evaluated descriptively. The patient will continue to take their usual standard of care drug(s) during the study; thus, there may be some variation in the standard of care regimens used by patients in the study.
Efficacy assessments	• Urine ACR • Urine PCR • eGFR (CKD-EPI formula (patients ≥ 18) or Creatinine-based "Bedside Schwartz" equation (2009) (in patients < 18)) • Progression of CKD
PK assessments	Crizanlizumab pre-dose/trough PK samples will be collected to accompany the immunogenicity samples in patients randomized to the crizanlizumab + standard of care arm to evaluate the impact of immunogenicity on exposure
Key safety assessments	• Monitoring and recording AEs based on Common Terminology Criteria for Adverse Events v5.0 • Laboratory assessments, including hematology, cytokines, complement, tryptase, p-selectin, clinical chemistry, and urinalysis • Vitals signs and physical examination • Electrocardiogram (ECG) • Immunogenicity (assessed only in patients randomized to crizanlizumab + standard of care) • Resource utilization due to AKI, VOCs, and/or other SCD complications

[redacted]

[redacted]

Data analysis	The primary endpoint, proportion of patients with ≥ 30% decrease in ACR at 12 months from baseline, will be descriptively summarized based on the data from the Full Analysis Set (FAS). A logistic regression model that includes effects for treatment and randomization stratification factors will be utilized. Patients will be stratified at randomization based on CKD risk category (moderate risk or high/very high risk) and HU/HC prescription (Yes/No). The treatment effect based on the log-odds ratio will be estimated by the model. The odds ratio for the relative difference between treatments in the primary endpoint, and its corresponding 95% confidence interval, will be presented. In addition, the proportions of patients in each group with at least a 30% decrease in ACR will be presented, along with a 95% 2-sided confidence interval for the difference in proportions. The secondary efficacy endpoints will be summarized using the FAS. The mean change in ACR from baseline will be analyzed using an Analysis of Covariance (ANCOVA) model that includes effects for treatment, randomization stratification factors, and baseline ACR. The slope of ACR decline and the slope of eGFR decline will be estimated as a random coefficient in a linear mixed effect model. For the percentage change in eGFR from baseline, an ANCOVA model that includes effects for treatment, HU/HC use (Yes vs No), and baseline eGFR, will be carried out for analysis using a logarithmic scale. The proportion related secondary efficacy endpoints will be descriptively presented by the same statistical methods described for the primary endpoint. For all safety analyses, the Safety Set will be used. AEs, vital signs, 12-lead ECG, clinical laboratory evaluations, immunogenicity data will be summarized. Annualized rate of visits to ER and hospitalizations due to AKI events, VOCs, or other SCD complications will be used to evaluate the healthcare resource utilization (visits to clinic, ER and hospitalizations) in crizanlizumab + standard of care arm and standard of care alone.
Key words	Sickle cell disease; sickle cell nephropathy; chronic kidney disease; albumin to creatinine ratio (ACR); albuminuria; estimated glomerular filtration rate (eGFR); protein to creatinine ratio (PCR); crizanlizumab + standard of care

[redacted]

1 Introduction

1.1 Background

1.1.1 Overview of sickle cell disease pathogenesis

Sickle cell disease (SCD) is a rare autosomal recessive blood disorder caused by a single missense mutation (Glu6Val) in the β-globin gene. It is the most common single gene disorder in African Americans, affecting approximately 1 in 375-600 people of African ancestry (Nietert et al 2002). Sickle cell disease is also common among people in Mediterranean countries, Africa, Middle East, India, Caribbean, and parts of South and Central America. The most severe forms of SCD are homozygous hemoglobin (Hb) S (sickle cell anemia) (HbSS) and the heterozygous form Hb S (HbS) with β-thalassemia (HbSβ^0-thal) (Ware et al 2017).

The Glu6Val mutation in the β-globin gene renders the mutant Hb less soluble and prone to polymerization upon deoxygenation. The polymerization of Hb causes deformation of red blood cells (RBCs) to give them a sickle shape (Bookchin and Lew 1996), and leads to chronic hemolysis, anemia, and vaso-occlusion (Wethers 2000). In SCD, sickled RBCs, leukocytes, platelets, and the endothelium are activated due to the chronic pro-inflammatory state. In turn, these circulating cells adhere to one another and to the microvasculature, resulting in vaso-occlusive events. Vaso-occlusion can in turn lead to vaso-occlusive crisis (VOC), which is the hallmark of the disease, as well as contributing to end organ damage (Powars et al 2005). Organ-specific vasculopathy often precedes clinical manifestations, decreases patient survival, and can occur in patients with SCD who do not have recurrent pain (Kassim and DeBaun 2013, Hoffmann et al 2013).

Common manifestations of SCD other than recurrent painful VOCs, include, but are not limited to chronic hemolytic anemia and chronic organ damage affecting the bones, brain, heart, kidneys, lungs, liver, spleen, eyes, and skin (Emerson and Lutty 2005, Sauntharajah and Vichinsky 2018). The manifestations of SCD start within the first few months of life as fetal Hb (HbF) levels decline as HbS levels increase.

Sickle cell disease is a complex disease and certain manifestations tend to be more common depending on the patient's age. For example, certain infections and manifestations involving the spleen tend to predominate in children aged between 1 and 3 years, between 12 and 20 years, strokes, priapism, and pain crises are predominant. More chronic complications such as renal insufficiency and pulmonary hypertension begin to appear in adults aged 20 to 30 years. Chronic Kidney Disease (CKD) and congestive heart failure are among the predominant manifestations in adults with SCD aged over 30 years.

Sickle cell nephropathy (SCN) refers to the spectrum of renal complications in SCD which first manifest in early childhood. Some patients progress to CKD, which is diagnosed when abnormalities of kidney structure or function are present for more than 3 months and is classified in five stages (1-5) according to the level of GFR (irrespective of underlying CKD etiology). The higher the CKD stage, the worse are the implications for health. Each stage is further categorized by the degree of albuminuria; increases in albuminuria are correlated with greater risk of progressing to a higher CKD stage, (KDIGO 2013). The prevalence of CKD in patients with SCD increases with age, is associated with poor outcomes and progresses to end-stage renal disease (stage 5) in around 12% of patients (Powars et al 2005; Gosmanova et

al 2014). Risk factors associated with increased mortality among patients with SCD include proteinuria and reduced eGFR; approximately 16 to 18% of overall mortality in these patients is attributed to kidney disease (Nath and Hebbel 2015). Development of SCN is complex and several pathophysiological mechanisms have been proposed to explain its development. Vaso-occlusion and hemolysis contribute substantially to the manifestations of SCN, which include glomerulopathies (such as hyperfiltration and proteinuria/albuminuria), hematuria, and tubular defects (Schnog et al 2004, Nasr et al 2006, Sharpe and Thein 2014, Hariri et al 2018). Focal segmental glomerulosclerosis (FSGS) and its variants are the major glomerular lesions.

Impaired urinary concentration and hyperfiltration are the earliest renal complications seen in patients with SCD. Hyperfiltration manifests as an increase in the glomerular filtration rate (eGFR) from a young age and can be defined as estimated GFR > 130 mL/min/1.73 m^2 (Yee et al 2017). Hyperfiltration is most common in younger individuals and is associated with markers of excess hemolysis and increased renal plasma flow, most likely due to increased effective glomerular filtration surface area (glomerular enlargement) caused by raised pressure within each glomerulus (Haymann et al 2010; Hirschberg 2010). Over time, this raised glomerular pressure results in damage to the glomerular filtration barrier, leading to albuminuria which can, over time, progress as the damage gets worse. Eventually, damaged glomeruli scar (sclerose) and the nephron associated with that glomerulus is lost. As more nephrons are lost, the total GFR falls back towards the normal range, though this is made up of higher single nephron GFRs in fewer total nephrons than in a healthy kidney. As the patient ages and this process continues, CKD progresses and the GFR continues to drop below the normal range as more nephrons are lost. As nephrons are lost, the pressure in the remaining nephrons increases exacerbating proteinuria and further decline. The proposed sequence of events described above, lead to worsening albuminuria and ultimately CKD and are mirrored in other causes of CKD such as diabetic nephropathy (Haymann et al 2017).

GFR is estimated from serum creatinine levels. The recommended equation for calculating eGFR is the CKD Epidemiology Collaboration (CKD-EPI) formula, which matches the accuracy of the Modification of Diet in Renal Disease (MDRD) equation at glomerular filtration rates (GFRs) < 60 mL/min/1.73 m^2 and offers greater accuracy at higher GFRs (Florkowski and Chew-Harris 2011). Further, among the typical estimating equations, the CKD-EPI formula appears to perform the best among sickle cell disease patients (Asnani and O'Neil Lynch 2013). The Creatinine-based "Bedside Schwartz" equation (2009) is recommended to calculate eGFR in those <18 years of age. The Schwartz equation to calculate eGFR in children has been recommended since 1970. Recent data shows that the original Schwartz formula overestimates GFR based on new methods of creatinine calculation and thus an updated equation was used to calculate GFR based on data from 349 children. This new formula called the "Bedside Schwartz" formula was noted to be the most accurate formula to avoid overestimation of eGFR in children (Schwartz et al 2009).

Microalbuminuria (30-300 mg/gram creatinine) is the earliest manifestation of hyperfiltration leading to glomerular injury in patients with SCD and marks the onset of sickle cell nephropathy (Bartolucci et al 2016). When assessed either as microalbuminuria or macroalbuminuria (> 300 mg/gram creatinine), proteinuria occurs in approximately 20% of patients in the first two decades, to 68% of older patients with HbSS (Guasch et al 2006; McPhearson et al 2011; Bartolucci et al 2016). Albuminuria is more common among patients with severe SCD

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genotypes (HbSS and HbSβ^0-thal) than milder genotypes (Guasch et al 2006; Derebail et al 2019) and is a strong predictor of subsequent progression of CKD (Sasongko et al 2015).

In a recent prospective, multicenter, longitudinal study evaluating 303 patients with SCA (HbSS and HbSβ^0-thal) it was noted that patients with baseline albuminuria ≥100 mg/g developed persistent albuminuria and reinforced that persistent albuminuria was associated with rapid eGFR decline and CKD development in adults with SCA (Niss et al 2020).

Patients with albuminuria and SCD also exhibit increased urinary excretion markers of tubular injury (kidney injury molecule-1 [KIM-1] and N-acetyl-β-D-glycosaminidase [NAG]) (Nath and Hebbel 2015). Acute kidney injury (AKI) has been found to occur in approximately 46% of patients with HbSS and HbSβ^0-thal, and AKI and AKI severity are independent risk factors for CKD progression (Saraf et al 2018).

1.1.2 Current treatment for sickle cell nephropathy

There are no prospective randomized data demonstrating a long term benefit of any treatments for SCD-related CKD and no treatments are approved for this indication. Thus, treatment for SCD-related CKD is currently based on data obtained from clinical situations outside of SCD and short-term studies in SCD. These treatments typically consist of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and/or hydroxyurea (HU)/hydroxycarbamide (HC).

Angiotensin converting enzyme inhibitors reduce glomerular pressure and are used extensively in a variety of clinical situations outside of SCD. It is common practice to administer ACE inhibitors for patients with SCN due to their renoprotective properties, but little is known about their effectiveness and safety in this setting. A Cochrane review revealed five studies evaluating ACE inhibitors in SCD patients but only one study with 22 adult participants met the criteria to be included in the review, a randomized or quasirandomized controlled trial of ACE inhibitors (captopril) designed to reduce microalbuminuria and proteinuria in patients with SCD compared to either placebo or standard treatment regimen (Sasongko et al 2015). At 6 months, there was no significant difference in urinary albumin excretion between the two groups, but the absolute change did show significant changes between the two groups, with a mean difference of 63 mg/24hours (95% confidence interval [CI]: -93.78 to -32.22). The authors of the Cochrane review concluded that though there is the potential for improvement with ACE inhibitors, there is not enough evidence to show that the administration of ACE inhibitors is associated with a reduction of microalbuminuria and proteinuria in patients with SCD (Sasongko et al 2015). More recently, in a study of 42 adult HbSS patients with SCN (urine albumin to creatinine ratio (ACR) > 10 mg/mmol, treatment with ACE inhibitors led to a decrease in ACR from baseline at 6 months of > 30% in 62% of patients (mean ACR: 46.4 ± 7.6 and 26.4 ± 3.9 mg/mmol at baseline and 6 months respectively; P = 0.002). Furthermore, an ACR decrease was detected at 1 month following initiation of ACE inhibitor treatment (32.9 ± 6.9, P = 0.02). Of note, approximately 45% of patients were also receiving concomitant hydroxyurea/hydroxycarbamide (HU/HC) (Haymann et al 2017).

The reduction of proteinuria after treatment with an ARB has been studied as a secondary endpoint in 1513 patients with Type 2 diabetes and nephropathy. Losartan (an ARB) reduced the level of proteinuria, with an average ACR reduction of 35% after an average of 3.4 years

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follow-up, whereas the urine ACR increased in the placebo group. The risk of end-stage renal disease was reduced by 28% with losartan versus the placebo group (Brenner et al 2001).

HU/HC is commonly used to treat SCD. Studies have indicated that HU/HC is associated with a lower prevalence of albuminuria in adults with SCD. In a cohort study of 58 adults with SCD who had not simultaneously received ACE inhibitors, the ACR in the patients taking HU/HC was significantly lower after 6 months of treatment with HU/HC with median ACR declining from 3.0 mg/mmol at baseline to 1.7 mg/mmol at 6 months. The results suggested that 6 months of HU/HC significantly attenuated the microalbuminuria observed during the early stages of SCN (Bartolucci et al 2016). Similarly, in a study of 149 adult patients with SCD, the prevalence of albuminuria (assessed by urine dipstick) was lower in the patients on HU/HC compared with patients not receiving HU/HC (34.7% vs. 55.4%, respectively; p = 0.01), as was median albumin excretion (17.9 mg/g vs. 40.5 mg/g; p = 0.04) (Laurin et al 2014).

1.1.3 Role of P-selectin in sickle cell disease

A component of the innate immune system, P-selectin initiates binding between leukocytes, platelets, and the endothelium at sites of inflammation during infection and injury. Normally this is a beneficial process, but when activation of these cells occurs unnecessarily or is excessive, P-selectin-mediated cell-cell interactions can cause a cascade of events culminating in disease. Multiple human and mouse studies relating to SCD have demonstrated that P-selectin initiates binding between sickled RBCs, leukocytes, platelets, and the microvasculature. Further, blockade of, or targeted gene knock out of, P-selectin abrogates these interactions and prevents vaso-occlusion. Please refer to the crizanlizumab Investigator's Brochure (IB) for details.

1.1.4 Introduction to crizanlizumab

1.1.4.1 Crizanlizumab (SEG101)

Crizanlizumab is a selective humanized monoclonal antibody (mAb) that binds to P-selectin with high affinity, blocking its interaction with its ligands, including P-selectin glycoprotein ligand-1.

Crizanlizumab was originally developed by Reprixys Pharmaceuticals Corporation under the investigational drug code SelG1 (completed studies SelG1-00003. Novartis study code: CSEG101A2101) and Se1G1-00005 (Novartis study code: CSEG101A2201). Novartis acquired the company on 18-Nov-2016, and is now the drug developer and sponsor for crizanlizumab, under the investigational drug code, SEG101. A Phase I study (CSEG101A2102) evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) comparability of SelG1 and SEG101 at 5 mg/kg and 7.5 mg/kg doses in healthy volunteers. Results are available from an ongoing Phase II study (CSEG101A2202) to assess the PK/PD of crizanlizumab with or without HU/HC in adult SCD patients with VOC (Section 4.5).

Crizanlizumab was first authorized in the US on 15-Nov-2019 and is now authorized in more than 40 countries for the prevention/reduction of VOCs in adults and pediatric patients aged 16 years and older with SCD under the invented names (Adakveo®/Ryverna®/Chylotrez®).

The approval was based on safety and efficacy data from the Phase II SUSTAIN study (Ataga et al 2017; see Section 1.1.4.2) below.

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The crizanlizumab IB provides detailed information related to toxicology, non-clinical pharmacology, drug properties, clinical and pre-clinical data.

1.1.4.2 Phase II Clinical Study (SUSTAIN study CSEG101A2201)

The objective of this pivotal, randomized, placebo-controlled study was to assess the safety and efficacy of crizanlizumab with or without HU/HC therapy in SCD patients with a history of VOC leading to a healthcare visit. A total of 198 SCD patients aged 16 to 63 years (inclusive), with any SCD genotype, a history of crises within the previous 12 months, and either with a steady dose of HU/HC or not taking HU/HC, were randomized 1:1:1 to crizanlizumab 5.0 mg/kg, crizanlizumab 2.5 mg/kg or placebo.

The median annual rate of VOC leading to a healthcare visit was 45.3% lower with 5 mg/kg crizanlizumab than with placebo (Hodges-Lehmann, median absolute difference of -1.01 versus placebo, 95% CI -2.00, 0.00). The difference between the 5 mg/kg arm and placebo arm was statistically significant (Wilcoxon rank sum test, $p = 0.010$). The median annual rate of uncomplicated crises and median number of days hospitalized, were 62.9% and 41.8% lower in the 5.0 mg/kg than in the placebo group, respectively. Crizanlizumab also delayed the time to onset of first and second VOC, and consistent benefit was further observed in a number of clinically relevant subgroups for the primary endpoint. Though patients on the 2.5 mg/kg dose showed reductions in VOCs, these were not statistically significantly different from placebo.

Crizanlizumab was generally well tolerated with similar incidence of treatment-emergent adverse events (TEAEs) across the three groups, and overall low incidence of discontinuations due to TEAEs (<5%). The proportion of patients experiencing serious adverse events (SAEs) was 25.8% at 5.0 mg/kg, 31.3% at 2.5 mg/kg, and 27.4% in the placebo group. There were five deaths during the study (two at 5.0 mg/kg, one at 2.5 mg/kg, and two in the placebo group), and none was deemed to be treatment-related. Please refer to IB for further information.

Overall, treatment of SCD patients with crizanlizumab at 5.0 mg/kg showed positive clinical activity as demonstrated by a statistically significant and clinically relevant decrease in the annual VOC rate compared with placebo and it was also found to be well tolerated (Ataga et al 2017). Accordingly, the recommended dose of crizanlizumab for future studies is 5 mg/kg dose and no studies are currently planned with the 2.5 mg/kg dose.

A post hoc analysis of the SUSTAIN data evaluated the development of proteinuria during the 12-month duration of the trial (Ataga et al 2018). Of the patients in the crizanlizumab group (both 2.5 mg/kg and 5 mg/kg arms combined) 35/106 (33%) developed proteinuria. In the placebo group 17/50 (34%) developed proteinuria. There was no association between the use of crizanlizumab and the risk of developing proteinuria (relative risk = 0.97, 95% CI 0.61-1.56). Note that proteinuria was measured by urine dipstick and ACRs were not measured. The number of patients with abnormal eGFR (defined as < 60 mL/min/1.73 m^2) and increased levels of serum creatinine was low in both treatment arms.

It is important to note that the SUSTAIN population was unselected with respect to CKD and approximately 20% of patients had proteinuria at baseline. Patients with any SCD genotype history could be eligible for SUSTAIN. Therefore, the SUSTAIN population was not consistent with a population in which crizanlizumab could be expected to provide a benefit by reducing proteinuria/albuminuria. Based on the information in Section 1.1.1, such a population for this

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current study ideally would consist of patients with severe SCD genotypes who have albuminuria and a rapid eGFR decline. Patients with hyperfiltration would need to be excluded to avoid confounding the study results.

1.2 Purpose

1.2.1 Study purpose and rationale

The purpose of this study is to explore the effect of P-selectin inhibition with crizanlizumab on renal function in SCD patients with CKD who are receiving standard of care for SCD-related CKD, have Grade A2-A3 albuminuria and Stage 1-3a CKD, and are at risk for rapid decline in their eGFR. Eligible patients will have an eGFR of ≥ 45 to ≤ 140 mL/min/1.73 m^2 and an ACR of ≥ 100 to < 2000 mg/g; based on previous studies, this population of patients will likely include patients with a rapid eGFR decline.

The study will evaluate descriptively, the effect of crizanlizumab + standard of care and standard of care alone on albuminuria (ACR) decrease at 12 months, as assessed by the proportion of patients with $\geq 30\%$ decrease in ACR at 12 months from baseline in patients with SCD-related CKD.

Based on the recommendation of a consensus panel focused on SCD end organ considerations specifically evaluating renal endpoints in SCD trials, albuminuria was recommended as a potential endpoint. The outcome measure suggested that was deemed clinically relevant was a 30% decrease in albuminuria evaluated by ACR (Farrell et al 2019). A meta-analysis of clinical trial data also suggests that each 30% decrease in geometric mean albuminuria by the treatment relative to the control was associated with an average 27% lower hazard for the clinical endpoint. This association strengthened after restricting analyses to patients with baseline albuminuria of more than 30 mg/g. The model from this analysis predicted that treatments that decrease the geometric mean albuminuria relative to the control group by 30% would have a high likelihood to confer clinical benefit (Heerspink et al 2019). See Section 8.3.5 for further details regarding the meta-analysis.

Previous trials conducted in patients with SCD-related CKD and non-SCD etiologies have evaluated drugs with varied mechanisms of action. ACE inhibitors, ARBs, and HU/HC have been evaluated in SCD-related CKD and other causes and have demonstrated a rapid decrease in proteinuria within 6 months. ACR was the most common measurement used to assess the reduction in proteinuria. The mechanism of action of ACE inhibitors in reducing albuminuria includes decreasing glomerular permeability to albumin (Sasongko et al 2015), that of ARBs is inhibiting angiotensin 1 signaling, which contributes to the glomerulopathy causing albuminuria, and though the mechanism is unknown for HU/HC it is hypothesized that it might result from decreased glomerular filtered load of albumin, improved glomerular permeability to macromolecules and it is thought that HU/HC might improve renal laboratory parameters by preventing VOCs that are associated with subclinical renal tubular injury (Bartolucci et al 2016). The reductions in ACR are limited to trials of 6 months duration and longer term data on the impact of decreasing proteinuria on progression of CKD are lacking.

The presence of P-selectin expression in the kidneys has been established based on in vitro and in vivo data, and there is evidence that P-selectin is upregulated in the kidney in response to

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renal ischemia-reperfusion injury in SCD (Zizzi et al 1997; Koo et al 1998; Singbartl et al 2000; Tam 2002).

A pre-clinical study was done to identify the role of P-selectin in ischemia-reperfusion-induced severe acute renal failure (Singbartl et al 2000). Mice with a null mutation in the P-selectin gene and wild type mice who received post-ischemic application of function-blocking monoclonal P-selectin antibody were studied. The P-selectin deficient mice had significantly smaller elevations in creatinine and blood urea nitrogen (BUN) concentrations after 24 and 48 hours of reperfusion. There was a significant reduction of neutrophil influx by 85% compared to wild type mice. In wild type mice, P-selectin was highly upregulated soon after reperfusion, reaching peak levels at 12 hours after reperfusion, at which time P-selectin was seen in the glomeruli (platelets and endothelial cells) and peritubular vessels (platelets), and to a lesser extent in the arteries and veins. The conclusions were that P-selectin was necessary to produce severe acute renal failure in response to ischemia-reperfusion. The authors also concluded that a causative role of P-selectin was further supported by the observation that neutrophil infiltration into post-ischemic kidneys was dramatically reduced in P-selectin deficient mice.

Expression of P-selectin in a glomerulonephritis induced mouse model was associated with rapid accumulation of neutrophils in glomeruli and significant proteinuria. P-selectin inhibition in this model was shown to abrogate glomerular neutrophil accumulation and prevented development of proteinuria (Tipping et al 1994).

Though this study provides pre-clinical evidence that P-selectin expression is linked to proteinuria, it is unknown if blocking P-selectin in the renal vasculature in vivo will have a beneficial impact on glomerulopathy and will delay the progression of CKD. Based on this limited data, the hypothesis is that administration of crizanlizumab, a P-selectin inhibitor, might have a beneficial effect in SCD patients with CKD by blocking P-selectin mediated multicellular adhesion (including leukocytes), and proteinuria, and also reducing vaso-occlusion and potentially its downstream effects in the renal vasculature, which can be clinically demonstrated by a decrease in proteinuria and slowing the decline in GFR. In evaluating crizanlizumab's impact on ACR reduction and eGFR decline over 1 year this will be correlated with progression of CKD during this 1-year period. If the study is able to demonstrate a positive effect of crizanlizumab on ACR reduction and the progression of CKD, this could provide positive evidence of a renoprotective effect of crizanlizumab.

[redacted]

In addition, in the general population, there is an association between worsening proteinuria and eGFR, and cardiovascular complications. Albuminuria is an established risk marker for both cardiovascular and renal outcomes (de Zeeuw et al 2004). Cardiovascular complications are increasingly evident in patients with SCD and CKD, and reducing albuminuria has the potential to provide a beneficial effect on various cardiac parameters, such as tricuspid regurgitation velocity (TRV) (Haymann et al 2017). [redacted]

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on albuminuria (ACR) decrease at 12 months	Proportion of patients with ≥ 30% decrease in ACR at 12 months from baseline
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on change in albuminuria (ACR)	Mean change in ACR from baseline to 3, 6, 9, and 12 months of treatment
To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on albuminuria (ACR) decrease at 6 months	Proportion of patients with ≥ 30% decrease in ACR at 6 months from baseline
To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on protein to creatinine ratio (PCR) at 12 months	Proportion of patients with PCR improvement and stable PCR (improvement: ≥ 20% decrease in PCR from baseline; stable: within ± 20% change from baseline) at 12 months from baseline
To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on the percentage change in eGFR	Percentage change in eGFR from baseline to 3, 6, 9, and 12 months of treatment
To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on ACR decline rate	Slope of ACR decline from baseline to 12 months of treatment based on ACR values at baseline and at 3, 6, 9, and 12 months
To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on eGFR decline rate	Slope of eGFR decline from baseline to 12 months of treatment based on eGFR values at baseline and at 3, 6, 9, and 12 months
To evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on the progression of CKD at 12 months	Proportion of patients with progression of CKD from baseline to 12 months
To evaluate descriptively overall safety and, tolerability of crizanlizumab + standard of care and standard of care alone	Safety will be assessed by the frequency and severity of adverse events (AEs), deaths, measurement of vital signs, ECG assessments, SAEs, and laboratory abnormalities
To assess the immunogenicity of crizanlizumab over the study period (treatment of 1 year + 105 days of follow-up)	Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab at select time points Crizanlizumab PK measurements will accompany immunogenicity measurements

[redacted]

Objectives	Endpoints
To evaluate descriptively healthcare resource utilization (visits to emergency room [ER] and hospitalizations) in crizanlizumab + standard of care arm and standard of care alone	Annualized rate of visits to ER and hospitalizations due to AKI events, VOCs, or other SCD complications

[redacted]

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g. premature discontinuation of treatment).

The primary clinical question of interest is: What is the effect of crizanlizumab + standard of care and standard of care alone on renal function in SCD patients with SCD-related CKD.

The primary estimand is described by the following attributes:

1. The target population comprises patients with kidney dysfunction due to SCD.
2. The primary variable is proportion of patients with ≥ 30% decrease in ACR at 12 months.

[redacted]

3. The treatment of interest is the effect of crizanlizumab 5.0 mg/kg + standard of care on the ACR value taken for the entire study duration with or without the intercurrent events.
4. The intercurrent events are the events occurring after randomization that may impact the treatment effect. The intercurrent events of interest are:
   a. Treatment discontinuation
   b. Initiation or discontinuation of HU/HC, HA approved form(s) of L-glutamine, ACE and/or ARB
   c. Intake of NSAIDs within 48 hours prior to ACR measurement
   d. Intake of voxelotor
   e. Blood transfusion or VOC occurred within 7 days of urine and blood sample collection
   f. Renal replacement therapy (i.e. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation)
5. The summary measure is the odds ratio of the treatment effect for patients with ≥ 30% decrease in ACR between crizanlizumab + standard of care and standard of care alone.

The detailed information regarding strategies on handling intercurrent events can be found in Section 12.4.3.

2.2 Secondary estimands

Not applicable.

3 Study design

This is a Phase II, multicenter, randomized two arm, open label study to evaluate descriptively the effect of crizanlizumab + standard of care and standard of care alone on renal function in SCD patients with SCD-related CKD.

The study will include patients ≥ 16 years of age with a confirmed diagnosis of SCD and SCD-related CKD. Homozygous HbS (HbSS sickle cell anemia) and HbSβ^0-thal SCD genotypes will be included. Patients eligible for the study will have:

- eGFR ≥45 to ≤ 140 mL/min/1.73 m2 based on the CKD/-EPI formula (in patients ≥ 18) and Creatinine-based “Bedside Schwartz” equation (2009) (in patients <18)
- ACR of ≥ 100 to < 2000 mg/g, despite standard of care treatment for SCD-related CKD

Eligible patients will be receiving standard of care drug(s) for SCD-related CKD according to institutional and local guidelines and the discretion of the physician. Any of the following drugs that the patient is receiving at study entry will be considered the patient’s standard of care: HU/HC, ACE inhibitors, and/or ARBs. The patient will continue to take their usual standard of care drug(s) during the study; thus, there may be some variation in the standard of care regimens used by the different patients in the study. Patients must have been receiving their standard of care drug(s) prior to study entry according to the dosing requirements in Table 6-1, and must plan to continue the same dose and schedule until the patient has reached the end of the study. The screening assessments will be done within 1 to 28 days prior to baseline (Week 1 Day 1).

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Overall, approximately 50 patients will be randomized 1:1 to receive either crizanlizumab (5 mg/kg) + standard of care or standard of care alone. Patients will be stratified at randomization based on CKD risk category (moderate risk or high/very high risk) and HU/HC prescription (Yes/No). The CKD risk categories used for stratification are based on both eGFR and albuminuria assessed by ACR as defined in Table 3-1:

Table 3-1 Prognosis of chronic kidney disease by glomerular filtration rate and albuminuria categories (chronic kidney disease risk categories)

	ACR (30-300 mg/g 3-30 mg/mmol) [1]	ACR (>300 mg/g > 30 mg/mmol)
eGFR ≥ 90 mL/min/1.73 m^2	1	2
eGFR 60-89 mL/min/1.73 m^2	1	2
eGFR 45-59 mL/min/1.73 m^2	2	3

1 = moderately increased risk; 2 = high risk; 3 = very high risk
[1] ACR ranges included above are according to KDIGO (2013); Note that patients in this study will have eGFR ≥ 45 to ≤ 140 mL/min/1.73 m^2 and ACR of ≥ 100 to < 2000 mg/g. Patients should be randomized based on ACR in mg/g.

Throughout this document, "study treatment" will refer to both treatment arms.

Patients randomized to crizanlizumab + standard of care will receive crizanlizumab by intravenous (i.v.) infusion over 30 minutes on Week 1 Day 1, followed by a second dose 14 days later (Week 3 Day 1), and then on Day 1 of every 4 weeks for a total on-study treatment period of 12 months in addition to their usual standard of care treatment. The visit for the assessment of the primary endpoint will take place on Week 53 Day 1. Patients will be followed up for two safety assessments 30 days (phone call) and 105 days (study visit) after the Week 51 Day 1 visit. Patients who will receive crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up. The end of the safety follow-up period for these patients will be the 30-day follow-up. All other patients are required to complete the 105-day follow-up.

Patients in the standard of care alone arm will continue to receive their usual standard of care treatment and will attend study visits per the same schedule as the patients randomized to crizanlizumab + standard of care (i.e., visits on Week 1 Day 1, Week 3 Day 1, then every 4 weeks up to Week 51 Day 1, followed by a visit on Week 53 Day 1 and two safety follow-up assessments 30 days phone call and 105 days study visit after Week 51 Day 1 [as applicable]).

Patients will discontinue the study due to unacceptable toxicity, death, or if they are lost to follow-up, and may also be discontinued from the study at the discretion of the investigator or patient if the study treatment is discontinued (however, please see Section 6.5.1 and Section 9.1 for further details). All patients who discontinue the study treatment early will attend an end of treatment (EOT) visit (visit EOT; within 7 days of the last dose of the discontinued study treatment) and be followed in the mandatory safety follow-up period, which includes safety assessments at 30 days (phone call) and 105 days (study visit, as applicable) after the last dose of the discontinued study treatment. These patients will also return for a mandatory Week 53

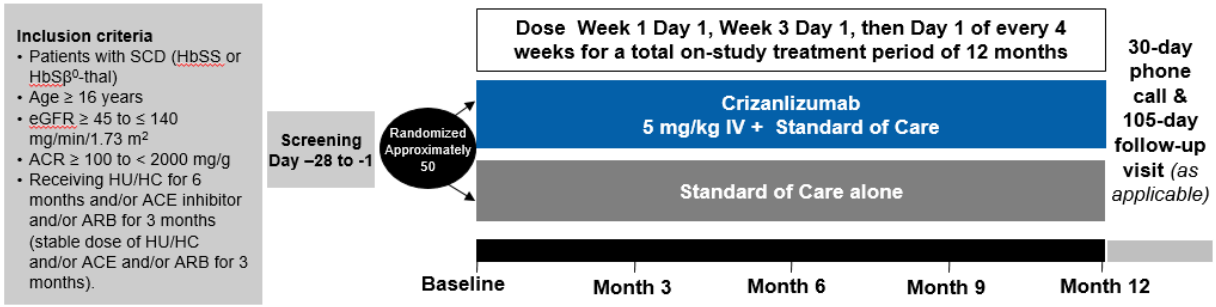
[redacted]

urine ACR/PCR assessment. The Week 53 urine ACR/PCR assessment should occur 12 months after the first dose of study treatment.

AEs will be recorded throughout the study. All patients will have hematologic, clinical chemistry and coagulation assessments done according to Table 8-1. Efficacy assessments of albuminuria (urine ACR) (see Section 8.3.1), PCR (Section 8.3.2), eGFR (Section 8.3.3), and progression of CKD (Section 8.3.4) will be assessed based on these laboratory assessments. [redacted] Electrocardiogram (ECG) assessments will be done at screening, at Week 53 Day 1, at visit EOT, and as clinically indicated. [redacted] In addition, patients randomized to the crizanlizumab + standard of care arm will have immunogenicity and PK assessments at select time points.

The study design is provided in Figure 3-1.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

The rationale for the study design is summarized in Table 4-1.

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Randomization (strata, allocation ratio)	Patients will be randomized 1:1 to receive either crizanlizumab + standard of care or standard of care alone. The 1:1 allocation ratio is acceptable as all patients will be receiving standard of care for SCD-related CKD, so it is not necessary to limit exposure to any of the treatment arms in this study.

[redacted]

	Chronic kidney disease stage and SCD treatment could affect ACR outcomes, so patients will be stratified at randomization based on CKD risk category and HU/HC prescription.
Blinding	This is an open label study as the benefits of a blinded study design incorporating a placebo infusion were deemed not to outweigh the burden to the study patients, particularly given the objective nature of the primary endpoint.
Duration of study periods	The treatment period will be 12 months, which should allow sufficient time to assess if crizanlizumab + standard of care provides additional decreases in ACR to standard of care alone per the primary study objective.

4.1.1 Rationale for choice of background therapy

In this study, crizanlizumab + standard of care will be descriptively evaluated to standard of care alone.

Patients with SCD and CKD will likely be receiving at least one of the following medications – HU/HC, ACE inhibitors, and/or ARBs, as established prior to study entry according to local practice and the discretion of the physician, and this will be considered their standard of care or background therapy. The patients will continue to take their usual standard of care drug(s) during the study. Thus, there may be some variation in the standard of care regimens used by the different patients in the study. Patients must have been receiving their standard of care drug(s) prior to study entry according to the dosing requirements in Table 6-1, and must plan to continue taking the drug(s) at the same dose and schedule until the patient has reached the end of the study. No dose modifications in standard of care medications can be made during the study, except for dose modifications due to AEs or weight adjustments at the discretion of the physician.

The assessment of crizanlizumab + standard of care to standard of care alone will enable the study patients to continue to receive and derive benefit from these medications. In blocking P-Selectin, crizanlizumab has a different mechanism of action compared with the standard of care medications. Therefore, this study will assess whether crizanlizumab is able to provide a clinically meaningful improvement in decreasing albuminuria in patients who have albuminuria and a rapid decline in eGFR, despite having received standard of care for at least 3 or 6 months prior to study entry.

4.2 Rationale for dose/regimen and duration of treatment

The 5 mg/kg dose of crizanlizumab, as well as the dosing schedule, to be used in this current study are supported by evidence from the SUSTAIN study.

The doses chosen for the SUSTAIN study (see Section 1.1.4.2 for further details) were based on P-selectin inhibition by crizanlizumab evaluated in healthy patients, as well as the acceptable safety experience observed in the Phase I study (CSEG101A2101).

The evidence of efficacy and safety on VOCs obtained from the Phase II SUSTAIN study supports the use of the 5 mg/kg dose in this current study.

[redacted]

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Patients with SCD and CKD will likely be receiving at least one of the following medications – HU/HC, ACE inhibitors, and/or ARBs, as established prior to study entry, and this will be considered their standard of care. The efficacy of crizanlizumab added to standard of care and standard of care alone will be descriptively evaluated.

A placebo-controlled study would allow a robust double-blind assessment of the efficacy of crizanlizumab added to standard of care. While acknowledging the limitations of an open-label study, the benefits of a blinded study design incorporating a placebo infusion were deemed not to outweigh the burden to the study patients for the current study. The open label nature of this study is considered acceptable as the assessment of the primary endpoint is based on an objective laboratory assessment, rather than a subjective measure.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

Please refer also to the latest version of the Investigator's Brochure for the most recent information on the efficacy and safety of crizanlizumab.

Results from the randomized, placebo-controlled SUSTAIN study in SCD patients (aged 16 years and older, any genotype) established the efficacy of crizanlizumab 5 mg/kg compared to placebo by showing a statistically significant and clinically meaningful reduction of the annual rate of VOC leading to healthcare visit. In addition, a more than a two-fold increase in the number of patients who remained completely free of VOC leading to healthcare visit during the study, and a three-fold increase in the median time to first VOC leading to healthcare was observed.

Thus, reduction in the rate of VOCs is a potential benefit for patients randomized to the crizanlizumab and standard of care arm in the current study, while acknowledging that this study population may have a lower background rate of VOCs than the SUSTAIN population.

Regarding the potential effect of crizanlizumab on renal function, based on pre-clinical studies evaluating P-selectin in the renal vasculature and the upregulation of P-selectin in response to ischemia-reperfusion injury, inhibiting P-selectin in the renal vasculature may confer additional benefit on the kidney. A post hoc analysis of SUSTAIN data showed no association between the use of crizanlizumab and the risk of developing proteinuria. However, the SUSTAIN population was unselected with respect to CKD and approximately 20% of patients had proteinuria at baseline. Thus, data evaluating a potential benefit of crizanlizumab in patients with preexisting renal disease due to SCD are lacking. Because vaso-occlusion contributes to the development of SCN leading to CKD, it is hypothesized that crizanlizumab, by inhibiting P-selectin mediated vaso-occlusion, could have a beneficial effect on renal function in SCD patients with CKD randomized to the crizanlizumab and standard of care arm in the current study. See Section 1.1.4.2 and Section 1.2.1 for further details. Patients randomized to either treatment arm (standard of care and crizanlizumab versus standard of care alone) could benefit from this study due to the close monitoring of renal and cardiac function planned for the study.

[redacted]

Pooled safety data from the SUSTAIN and CSEG101A2202 studies in patients treated with crizanlizumab 5 mg/kg (n=111 patients, Oct 2019 cutoff) showed that crizanlizumab is generally associated with a favorable safety profile. Adverse drug reactions (ADRs) were arthralgia (17.1%), nausea (16.2%), pyrexia (14.4%), back pain (14.4%), abdominal pain (10.8%), diarrhea (9.0%), pruritus (7.2%), vomiting (6.3%), myalgia (5.4%), musculoskeletal chest pain (4.5%), oropharyngeal pain (4.5%), infusion site reaction (2.7%), and infusion-related reaction (2.7%). These ADRs may be signs and symptoms of an infusion related reaction when observed during/within 24 hours of an infusion.

In addition, in the randomized SUSTAIN study the overall frequency of AEs, SAEs and AEs leading to treatment discontinuation was similar among patients treated with crizanlizumab 5 mg/kg and placebo. Use of crizanlizumab in combination with HU/HC did not result in any meaningful differences in the safety profile.

Based on class effects, pre-/clinical findings, and the mechanism of action of crizanlizumab, identified and potential risks include the following:

Infusion-related reactions (IRRs)

Administration of monoclonal antibodies (mAbs) can be associated with IRRs. A focused search for potentially "severe" IRRs (i.e. indicative of hypersensitivity/anaphylaxis or cytokine-release syndrome) identified 3 (2.7%) patients treated with crizanlizumab 5 mg/kg in the pooled data set. The event reported for all 3 patients was "infusion-related reaction," none of which was severe (all Grade 1 or 2, all non-serious), none required hospitalization or treatment discontinuation, and all events resolved without sequelae or complications on the same day.

However, severe IRRs including cases requiring hospitalization have been described in ongoing clinical trials and in the post-marketing setting. Refer to Investigator's Brochure for additional details regarding these IRRs.

Additionally, a broad search for IRRs using an extensive list of potential signs and symptoms related to infusion reactions, and occurring within 24 hours of the infusion, identified 37 patients (33.3%) in the safety pool with at least one event. Most of these events were reported in 1 or 2 patients only, except for nausea (9.0%), headache (9%), arthralgia (6.3%) and back pain (4.5%), and fatigue, hypertension, dizziness and myalgia (2.7%). None of the events were grade 3 or 4 in severity. In the SUSTAIN study, IRRs using this broader search were more frequent in the 5 mg/kg arm (34.8%) compared to the placebo arm (21.0%). However, except for nausea, none of the events were reported with an absolute differences of more than 5% in the crizanlizumab 5 mg/kg vs. the placebo arm and none was severe. Based on post marketing reports, IRRs may present as pain, refer to Investigator's Brochure for additional details.

In summary, current data suggest that administration of crizanlizumab can be associated with IRRs, including pain events, some of which can be severe and/or require hospitalization. Participants should be monitored for potential signs and symptoms of IRRs, and participants instructed to contact the investigator/site when experiencing such events. In case of severe IRRs (eg. hypersensitivity/anaphylactic reaction), study treatment should be discontinued.

Immunogenicity

Administration of mAb can be associated with immunogenicity, including development of anti-drug antibodies (ADA) or hypersensitivity following treatment with crizanlizumab (see above).

[redacted]

In clinical studies, treatment-emergent ADAs were transiently detected in 1 patient among the 111 patients who received crizanlizumab 5 mg/kg (0.9%). There was no evidence of an altered PK/PD or safety profile with ADA development.

Infections

Based on the mechanism of action and physiological role of P-selectin, crizanlizumab could potentially be associated with an increased infection risk.

Infection-related AEs (based on all preferred terms included in the system organ class "Infections") were reported in 49.5% patients in the safety pool. The most frequently reported infections were urinary tract infection (11.7%), upper respiratory tract infections (9.9%), pneumonia (4.5%) and sinusitis (3.6%). Most infections were low in severity (grade 1 or 2). In the randomized SUSTAIN study, infection-related AEs was similar across the arms: 53.0% in the crizanlizumab 5 mg/kg and 53.2% in the placebo arm. In addition, there was no difference between the arms in the incidence of neutropenia or white blood cell counts.

In summary, no increased frequency or severity of infections has been observed in clinical studies with crizanlizumab so far, suggesting that crizanlizumab has no clinically relevant effect to induce or complicate infections in SCD patients. However, investigators are advised to monitor patients for signs/symptoms of infections; patients further should have received standard age-appropriate care for SCD, including penicillin prophylaxis and immunizations (refer to eligibility criteria of the protocol).

Effect on hemostasis

Considering the mode of action of crizanlizumab and physiological role of P-selectin, a potential effect on the hemostatic system was evaluated by searching for AEs related to hemorrhage, or abnormal laboratory parameters. In the safety pool, a search for hemorrhagic events identified 16 (14.4%) patients, mostly related to abnormal laboratory findings. Except for prolonged prothrombin time (PT), decreased hemoglobin, and epistaxis, reported in 3 (2.7%) patients each, these events were reported in 1 or 2 patients only. None were grade 4 or led to study withdrawal, and none were considered treatment related as per investigator assessment. The only grade 3 event was decreased hemoglobin (2 patients), consistent with hemolysis and the underlying disease.

In Study A2201, hemorrhagic events were reported in 11 (16.7%) patients in the 5 mg/kg and 8 (12.9%) patients in the placebo arm, mostly related to laboratory abnormalities. Of note, 1 event (intracranial hemorrhage) reported in the 2.5 mg/kg arm was considered serious (grade 4, hospitalization) and led to study drug discontinuation. Cerebrovascular accidents, including hemorrhagic stroke, are known complication and leading cause of death in patients with SCD.

In summary, bleeding events were rare, with the majority of the observed AEs being abnormal laboratory parameters on single occasions. The available data do not suggest an adverse effect of crizanlizumab on hemostasis. Nevertheless, patients should be monitored for signs/symptoms of bleeding; additionally, hematology and coagulation parameters will be regularly assessed during the study.

A separate search for potential AEs related to thrombosis did further not identify any patients with AEs related to thrombosis in the 5 mg/kg pooled data, suggesting that crizanlizumab does not have relevant a pro-aggregant or pro-thrombotic effect.

[redacted]

Laboratory test interference with automated platelet counts

Interference with automated platelet counts (platelet clumping) has been observed in patients treated with crizanlizumab in clinical studies, in particular when tubes containing EDTA were used. This may lead to unevaluable or falsely decreased platelet counts. Current clinical and pre-clinical data suggest this is an ex vivo effect that is EDTA- and time-dependent, without indication of platelet clumping, true reduction in circulating platelets or pro-aggregant effect in vivo.

QT prolongation and hepatic safety

Based on the data generated to date, crizanlizumab does not have a clinically relevant effect on QT interval, and there is no evidence for severe or drug-induced hepatotoxicity.

Pregnancy and lactation

The potential risk to pregnant women is unknown, and there are no adequate and well-controlled studies in pregnant women to inform the associated risk. Animal reproduction studies in cynomolgus monkeys have not shown embryofetal toxicity or risk of increased fetal abnormalities with IV administration of crizanlizumab during gestation at doses up to 50 mg/kg (approximately 16 times the human clinical exposure based on AUC in patients with SCD at 5 mg/kg once every 4 weeks). There was a numerical increase in fetal losses, the cause of which is unclear and may be related to development of antibodies against crizanlizumab in monkeys. No maternal toxicity was observed.

Pregnant or breastfeeding women as well as those of childbearing potential (unless using effective contraception) will not be allowed to participate in the study. Please refer to the Eligibility criteria of the protocol for details.

Monoclonal antibodies and male fertility

Regarding male fertility, IgG monoclonal antibodies can distribute to seminal fluid, however to an extent approximately one log lower than what could maximally be observed for a small molecule (Scialli et al 2015, Banholzer et al 2016). A clinical trial of denosumab, an IgG2 monoclonal antibody in healthy male volunteers showed that denosumab was measurable at low concentrations in seminal fluid (approximately 2% of serum concentrations, Sohn et al 2015). Data indicate that male-mediated mAb drug transfer via the semen provides negligible exposure of the mother to the mAb and that the mAb is not bioavailable to the fetus. Based on the pharmacokinetic features of IgG monoclonal antibodies including low distribution to the semen and very low absorption in the vagina, the expected mAb dose to the fetus via seminal drug delivery to the vagina would be approximately 10,000 to 30,000 fold lower than by intravenous dosing. Thus the potential of fetal harm from semen delivery of a monoclonal antibody is currently considered to be biologically implausible (Breslin et al 2014).

Appropriate eligibility criteria and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.5. The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures and close clinical monitoring. If deemed clinically necessary, participants optionally could be kept in-the hospital for 24 hours following an investigational treatment dose.

There may be unforeseen risks with crizanlizumab, which could be serious.

[redacted]

While the safety of crizanlizumab has been studied in patients with SCD, it has not been specifically studied in a population of patients with SCD-related CKD.

In summary, the sponsor considers that the benefit-risk ratio for conducting this study is favorable.

COVID-19 pandemic
No substantial additional risk for patients due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified at this time and therefore the benefit risk remains unchanged. In case of active COVID-19 infection, please refer to Section 6.5.1 Dose Modifications. The risk/benefit balance will be re-evaluated as and when required whilst the COVID-19 pandemic continues.

5 Population

This study is designed to enroll approximately 50 SCD patients aged ≥ 16 years with SCD-related CKD. Homozygous HbS (HbSS sickle cell anemia) and HbSβ^0-thal SCD genotypes are eligible. Eligible patients will have an eGFR of ≥ 45 to ≤ 140 mL/min/1.73 m^2 and an ACR of ≥ 100 to < 2000 mg/g; based on previous studies, this population of patients will likely comprise patients with a rapid eGFR decline.

The investigator or designee must ensure that only patients who meet all of the inclusion and none of the exclusion criteria are offered treatment in this study.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Male and female patients ≥ 16 years on the day that signed informed consent is obtained
3. Confirmed diagnosis of SCD by Hb electrophoresis (performed locally, or by a central laboratory if the country does not have local capabilities) or high performance liquid chromatography (performed locally). Homozygous HbS (HbSS sickle cell anemia) and HbSβ^0-thal SCD genotypes are eligible
4. Patients with eGFR ≥ 45 to ≤ 140 mL/min/1.73 m^2 based on CKD EPI formula (patients ≥ 18) or the Creatinine-based "Bedside Schwartz" equation (patients < 18)
5. Patients with ACR of ≥ 100 to < 2000 mg/g (taken as an average of the three screening ACR values to determine eligibility).
6. Receiving at least 1 standard of care drug(s) for SCD-related CKD according to local guidelines. If receiving HU/HC, the patient must have been receiving HU/HC for at least 6 months and on a stable dose for 3 months prior to study entry. If receiving an ACE inhibitor and/or ARB the patient must have been receiving the drug for 3 months and also on a stable dose for those three months prior to study entry, in all cases, patients must plan to continue taking the drug(s) at the same dose and schedule until the patient has reached the end of the study.
7. Hb ≥ 4.0 g/dL, absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L, and platelet count ≥ 75 x 10^9/L
8. Patients who are clinically stable and are in a non-crisis state at the time of enrollment

[redacted]

9. Adequate hepatic function as defined by:
   - Alanine aminotransferase (ALT) < 3.0 x upper limit of normal (ULN)
   - Direct (conjugated) bilirubin ≤ 3.0 x ULN
10. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.0
11. Up-to-date record of immunizations, as per local requirements

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. History of stem cell transplant
2. Patients with evidence of AKI within 3 months of study entry (can decrease interval to within 6 weeks of study entry only if renal function has returned to pre-AKI values prior to study entry)
3. Blood pressure > 140/90 mmHg despite treatment
4. Body mass index of ≥ 35
5. Patients undergoing renal replacement therapy (ie. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation)
6. Received blood products within 30 days of Week 1 Day 1
7. Participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes). Transfusions for acute complications are permitted (acute chest syndrome [ACS], acute splenic sequestration, acute hepatic sequestration, worsened anemia)
8. History of kidney transplant
9. Patients with hypoalbuminemia defined as <25 g/L
10. Contraindication or severe hypersensitivity to any drug or metabolites from similar class as crizanlizumab or to any excipients of the crizanlizumab formulation
11. History of severe hypersensitivity reaction to other mAb, which in the opinion of the investigator may pose an increased risk of serious infusion reaction
12. Patient has received crizanlizumab and/or other selectin inhibitor or plans to receive it during the duration of the study.
13. Currently on voxelotor or received voxelotor within 6 months of screening.
14. Use of HA approved form(s) of L-glutamine within 6 months of screening, unless it has been used at a stable dose for the full 6 months
15. Received an investigational compound within 30 days (or 5 half-lives of that agent, whichever is greater) prior to screening
16. Uncontrolled diabetes
17. Concurrent severe and/or uncontrolled medical conditions which, in the opinion of the investigator, could cause unacceptable safety risks or compromise participation in the study
18. Clinically significant bleeding disorder
19. Significant active infection or immune deficiency (including chronic use of immunosuppressive drugs)
20. Patient with active human immunodeficiency virus (HIV) infection (detectable viral load)

[redacted]

21. Patients with active Hepatitis B (HBV) infection (hepatitis B surface antigen [HbsAg] positive) will be excluded

    Note: Patients with antecedent but no active HBV (i.e., hepatitis B core antibody [HbcAb] positive, HbsAg and HBV-deoxyribonucleic acid negative) are eligible
22. Positive test for hepatitis C (HCV) ribonucleic acid (RNA)

    Note: Patients in whom HCV infection resolved spontaneously (positive HCV antibodies without detectable HCV RNA) or those that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA ≥ 6 months (with the use of interferon [IFN]-free regimes) or ≥ 12 months (with the use of IFN-based regimes) after cessation of antiviral treatment are eligible
23. Malignant disease. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 3 years prior to study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma *in situ*
24. History of or current diagnosis of ECG abnormalities indicating significant risk of safety such as:
    - Concomitant clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), and clinically significant second or third degree atrioventricular block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsade's de Pointes
25. Evidence of CKD attributed to causes other than SCN
26. Obstructions of the urinary tract
27. Current drug or alcohol abuse as per investigator discretion.
28. Pregnant or nursing (lactating) women
29. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study, and for patients randomized to crizanlizumab + standard of care, for 15 weeks after stopping crizanlizumab. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 6 weeks before Week 1 Day 1. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before Week 1 Day 1.

[redacted]

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms). Women are considered not of childbearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks prior to Week 1 Day 1. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

No additional exclusions should be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Note: The investigator has the discretion to include/exclude a patient in the study, who will be found to have symptoms representative of COVID-19 or tested positive for COVID-19 during the screening phase. Such patients should be managed as per the country specific guidelines related to COVID-19. For patients who test positive for COVID-19, re-testing is recommended before initiating study treatment.

6 Treatment

6.1 Study treatment

Patients will be randomized into one of two treatment arms, crizanlizumab + standard of care, or standard of care alone.

Novartis will supply crizanlizumab (SEG101) as an open label medication. Patients in the crizanlizumab + standard of care arm will receive crizanlizumab dose of 5.0 mg/kg by i.v. infusion over 30 minutes on Week 1 Day 1, followed by a second dose 14 days later (Week 3 Day 1), and then every 4 weeks for a total on-study treatment period of 12 months in addition to their usual standard of care treatment. Patients in the standard of care alone arm will continue to receive their usual standard of care treatment.

Study sites will continue to source the standard of care drug(s) for SCD-related CKD that the patient was receiving at study entry according to institutional and local guidelines and the discretion of the physician. Any of the following drugs that the patient is receiving at study entry will be considered the patient's standard of care (patients included in this study must have been receiving at least one of the following): HU/HC, ACE inhibitors, and ARBs. The dosing requirements for these drugs prior to study entry are provided in Table 6-1.

Table 6-1 Standard of care drugs

Drug or drug class[1]	Required minimum duration of treatment prior to study entry	Required minimum duration on stable dose prior to study entry
Hydroxyurea (HU)/Hydroxycarbamide (HC)	6 months	3 months
Angiotensin-converting enzyme (ACE) inhibitor	3 months	3 months

[redacted]

Angiotensin-receptor blocker (ARB)	3 months	3 months

[1] Patients included in this study must have been receiving at least one of the drugs listed in this table

The patient will continue to take their usual standard of care drug(s) during the study; thus, there may be some variation in the standard of care regimens used by patients in the study. If receiving HU/HC the patient must have been on the drug for 6 months prior to study entry and on a stable dose for 3 months. If receiving an ACE inhibitor and/or ARB, the patient must have been receiving drug and on a stable dose for 3 months prior to study entry. In all cases, patients must plan to continue taking the drug(s) at the same dose and schedule until the patient has reached the end of the study. No dose modifications in standard of care medications may be made during the study, except for dose modifications due to AEs or weight adjustments at the discretion of the physician (see Section 6.5.1.2). Standard of care medication(s) being taken by the patient at the time of Interactive Response Technology (IRT) enrollment will be recorded in the Dosage Administration Record (DAR) electronic Case Report/Record Form (eCRF). Evidence that the patients have been receiving the standard of care medication(s) at a stable dose should be documented in the source documents.

Starting any new treatment with HU/HC within 6 months and ACE inhibitor and/or ARB within 3 months prior to screening, up to the end of the study is prohibited and will be a protocol deviation (see Section 6.2.2).

6.1.1 Crizanlizumab

Crizanlizumab will be supplied in single use vials containing 10 mL at a concentration of 10 mg/mL. One vial contains 100 mg of crizanlizumab.

The patient will receive up to 14 doses of crizanlizumab by i.v. infusion, which will take approximately 30 minutes. Crizanlizumab must not be administered by i.v. push or bolus. On infusion day, the pharmacist or designated personnel will compound crizanlizumab in accordance with the Pharmacy Manual. See Table 6-2 for details of crizanlizumab.

Table 6-2 Crizanlizumab

Drug	Dose	Pharmaceutical Dosage Form and Route of Administration	Frequency and/or Regimen	Supply Type
Crizanlizumab (SEG101)	5.0 mg/kg	Concentrate for solution for infusion. i.v. infusion	Week 1 Day 1 Week 3 Day 1 Day 1 of every 4-week cycle	Open label vials

6.1.2 Additional study treatments

No other treatment beyond crizanlizumab and standard of care are included in this trial.

6.1.3 Treatment arms/group

Patients will be randomly assigned at the Week 1 Day 1 visit to one of the following treatment arms in a 1:1 ratio:

[redacted]

- Crizanlizumab + standard of care
- Standard of care alone

6.1.4 Guidelines for continuation of treatment

Refer to Table 6-3 for criteria for re-initiation of investigational drug following dose interruptions due to certain ADRs.

6.1.5 Treatment duration

The planned duration of treatment is 12 months. Patients will discontinue study treatment (crizanlizumab and/or at least one standard of care drug, as applicable) early due to unacceptable toxicity, and/or if study treatment is discontinued at the discretion of the investigator or the patient. Please see Section 9.1 on discontinuation of study treatment.

Patients who are deriving benefit from crizanlizumab based on the investigator's evaluation may receive access to crizanlizumab post-trial as indicated in Section 9.2. In addition, patients randomized to the standard of care alone arm may receive post-trial access to crizanlizumab as per investigator discretion if benefit is demonstrated for patients in the crizanlizumab + standard of care arm.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited. The patient must notify the study site about any new medications he/she takes within 30 days prior to initial dosing (i.e., within 30 days prior to Week 1 Day 1) until the completion of the safety follow-up period (i.e., 30-day safety follow-up or the 105-day follow-up visit [as applicable]).

All medications (including prescription drugs, herbal medications/supplements, over the counter [OTC] medication, dietary and vitamin supplements) and significant non-drug therapies (including physical therapy and blood transfusions) taken or administered within the timeframe defined in the entry criteria until completion of the safety follow-up period must be listed on the Prior and Concomitant medications, Surgical and Medical Procedures or Transfusion page of the eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If the patient is already randomized, contact Novartis medical monitor to determine if the patient should continue participation in the study.

Concomitant treatment with erythropoietin -stimulating agents (ESA), aspirin, NSAIDs, and prophylactic doses (as per local guidelines) of anticoagulants are permitted, while other anti-platelet agents or anticoagulants at doses targeting therapeutic levels should be used with caution (refer to Section 6.2.1.1). All approved forms of analgesia for pain are permitted as per physician's discretion. Note that NSAID use should be avoided within 48 hours prior to ACR

measurements. Other approved medications for supportive care (antiemetics, anxiolytics, hypnotics, antihistamines) are permitted, including marinol.

Oral contraceptives are permitted in this study at the discretion of the investigator (see the contraception requirements outlined in the exclusion criteria (Section 5.2).

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Although transfusion of blood components is permitted (i.e., transfusions for acute complications [ACS], acute splenic sequestration, acute hepatic sequestration, worsened anemia), it is unclear how such transfusions will impact the PK/PD of crizanlizumab, so investigators are encouraged to obtain PK and PD samples before and after each transfusion session when possible; in this case, please contact the Novartis medical monitor. It should also be considered that the administration of products containing immunoglobulins (plasma, IVIG, anti-globulins) may also impact the efficacy of crizanlizumab, and optional PK and PD testing may also be performed prior to and following administration of such therapies.

If a patient requires renal replacement therapy (i.e. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation), study treatment should be discontinued. Renal replacement therapy should be recorded on the appropriate eCRF.

L-glutamine is approved in the United States to reduce the acute complications of SCD in adult and pediatric patients 5 years and older.

HA approved forms(s) of L-glutamine is permitted if the patient has been receiving a stable dose for at least 6 months prior to screening and plans to continue taking it at the same dose and schedule until the patient reaches the end of the study. Although HA approved form(s) of L-glutamine is permitted, other OTC forms of L-glutamine are discouraged, as are other natural and herbal remedies (e.g., EvenFlo and/or products containing dang gui, ligustrum root, ginseng root, white peony, corydalis, salvia, copodonosis, poria, jujube, angelica sinensis, lovage) are discouraged due to the unproven efficacy and variable quality and composition of these products. Vitamin and mineral supplements (e.g., fish oil, folic acid, L-arginine, L-citrulline, magnesium, riboflavin, vitamin C, vitamin D, vitamin E, and zinc) are also permitted, though caution is advised when taking amounts exceeding 100% of the recommended daily allowance.

Avoid any live vaccines against infectious diseases within 4 weeks prior to Week 1 Day 1. There is no restriction on the administration of inactivated vaccines during the study.

Anti-platelets agents or anticoagulants at therapeutic doses should be used with caution due to a potential effect of P-selectin inhibition on hemostasis.

Infusion related reactions have been observed with crizanlizumab administration.

Prophylactic pre-medication is permitted, and sites should follow local practice and guidelines for administration of monoclonal antibodies; pre-medications may be adjusted based on clinical presentation as deemed appropriate (e.g. for pain management).

If a participant experiences a Grade 3 or 4 infusion related reaction, the study treatment must be discontinued.

Steroids should be used with caution, and when clinically indicated (e.g. to manage hypersensitivity/anaphylactic reactions). There is no existing clinical data on concomitant use

[redacted]

of crizanlizumab and corticosteroids. For patients presenting for acute pain related to sickle cell disease, the 2020 guideline from American Society of Hematology suggests against corticosteroids for acute pain management (Brandow et al, 2020)

Please refer to Table 6-3 for further guidance on management of IRRs.

6.2.2 Prohibited medication

The use of investigational drugs other than crizanlizumab is prohibited during the study. The use of voxelotor is also prohibited during the study, as are stem cell transplants. In addition, the administration of mAb other than crizanlizumab is prohibited, due to the theoretical potential for cross-reactivity and/or overlapping toxicities with other mAb.

If investigational agents have been used in the past, they must have been discontinued at least 30 days (or 5 half-lives of that agent, whichever is greater) prior to screening. Patients that have received prior treatment with crizanlizumab are not allowed to enroll in this study.

Voxelotor was approved by FDA on 25-Nov-2019 for the treatment of sickle cell disease (SCD) in adult and pediatric patients 12 years of age and older. The impact of voxelotor on renal function is unknown, so use of voxelotor within the last 6 months prior to screening or current use of voxelotor is prohibited in this study.

Abuse of drugs or alcohol is also prohibited during the study.

Starting any new treatment with HU/HC, HA approved form(s) of L-glutamine, within 6 months prior to screening and ACE inhibitors or ARBs within 3 months prior to screening up to the end of the study is prohibited and will be recorded as a protocol deviation. Note that any new treatment with HU/HC, HA approved form(s) of L-glutamine, ACE inhibitors, and/or ARBs started on or after Week 1 Day 1 will be recorded on the Concomitant Medications eCRF; they will not be recorded on the DAR eCRF. If any new treatment with HU/HC, HA approved form(s) of L-glutamine, ACE inhibitors, and/or ARBs is started during the study, changes should not lead by default to discontinuation of the patient from the trial (see Section 9.1); however, the Novartis medical monitor must be notified.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

Each patient will be identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential Patient No. suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the ICF, the patient is assigned to the next sequential Patient No. available.

6.3.2 Treatment assignment, randomization

At visit “Week 1 Day 1” all eligible patients will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will complete the eligibility checklist in IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm.

[redacted]

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of Patient Numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers, as applicable. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the assignment of medication numbers to packs containing the study treatment.

Following the decision to stop recruitment, approximately 50 SCD patients will be randomized in a 1:1 ratio to either 5.0 mg/kg of crizanlizumab + standard of care, or standard of care alone.

Patients will be stratified at randomization based on CKD risk category (moderate risk or high/very high risk) and HU/HC prescription (Yes/No).

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

This is an open label study and no blinding will be applicable. Investigators, patients and sponsor have full knowledge of treatment allocation. In order to minimize the potential impact of treatment knowledge, until the final analysis is conducted, no aggregate statistical analysis (efficacy and safety across the study) shall be performed by treatment other than DMC safety review outputs which will be performed by independent programmer. Details of the data reviewed by the Clinical Trial Team (CTT) will be specified in the Data Quality Plan.

Randomization codes and the full randomization list will be kept strictly confidential until the time of safety analyses for DMC and the final analysis.

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

6.5.1.1 Crizanlizumab

For patients who do not tolerate the protocol-specified dosing schedule, crizanlizumab dose interruptions are either recommended or mandated. Dose reductions are not allowed.

If a patient experiences drug-induced toxicity, the patient should be closely monitored and a decision to continue or discontinue the patient from the study should be made at the next dose scheduled.

These dose interruptions are summarized in Table 6-3. Deviations to mandatory dose interruptions are not allowed. Permanent treatment discontinuation is mandatory for specific events as indicated in Table 6-3. Every effort should be made to maintain the patient on the protocol-defined dosing schedule. In case of dose delay for any reason, the dose should be given as soon as possible. If that infusion visit occurs within ± 7 days of a protocol-scheduled visit, then the dose and all required assessments will be assigned to the nearest protocol-scheduled visit. However, if that infusion visit does not fall within ± 7 days of a protocol-scheduled visit, the dose and corresponding assessments will be documented as an unscheduled visit. At that

[redacted]

point, every effort should be made to bring the patient's infusions back onto the protocol defined schedule (within the ± 7 day window). All doses of crizanlizumab (except the Week 3 Day 1 loading dose) must be separated by at least 21 days from the prior dose. If a patient misses two consecutive doses of crizanlizumab due to ADR; i.e., an AE attributable to study drug), the patient should be discontinued from crizanlizumab. Patients with Grade 3 and 4 IRRs will be permanently discontinued from crizanlizumab and patients with other specified grade 4 ADRs will be permanently discontinued from crizanlizumab. Crizanlizumab dose interruptions must be recorded on the Study Treatment- Infusion eCRF.

Table 6-3 Criteria for dose interruption and re-initiation of crizanlizumab due to adverse drug reactions

Dose interruption and re-initiation of crizanlizumab	
Worst toxicity **CTCAE[a] Grade (CTCAE Version 5.0) during a cycle of therapy**	**Action on dose interruption and re-initiation of crizanlizumab**
Investigations (hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < lower limit of normal [LLN] – 1500/mm^3) and Grade 2 (ANC < 1500 – 1000/mm^3)	No action, continue treatment.
Grade 3 (ANC < 1000 – 500/mm^3)	**Mandatory:** Interrupt dose until resolved. If abnormality persists, permanently discontinue the patient from the study.
Grade 4 (ANC < 500/mm^3)	**Mandatory:** Permanently discontinue the patient from the study.
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	**Mandatory:** Interrupt dose until resolved or next dose schedule. If abnormality persists, permanently discontinue the patient from the study.
Thrombocytopenia	
Grade 1 (LPT < LLN – 75,000/mm^3) and Grade 2 (LPT < 75,000 – 50,000/mm^3)	No action, continue treatment.
Grade 3 (LPT < 50,000 – 25,000/mm^3)	Recommendation: Interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists, permanently discontinue the patient from the study.
Grade 4 (LPT < 25,000/mm^3)	**Mandatory:** Permanently discontinue the patient from the study.
Investigations (hepatic)	
Isolated direct bilirubin	
Grade 1 (> ULN – 2.0 x ULN)	No action, continue treatment.
Grade 2 (> 2.0 – 3.0 x ULN) and Grade 3 (> 3.0 – 10.0 x ULN)	Recommendation: interrupt dose. Monitor liver function tests (LFTs)[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline. Monitor for hemolysis. If resolved, then continue with next dose scheduled.
Grade 4 (> 10.0 x ULN)	**Mandatory:** Permanently discontinue the patient from treatment.
Isolated ALT elevation	
Grade 1 (> ULN – 3.0 x ULN)	No action, continue treatment.
Grade 2 (> 3.0 – 5.0 x ULN)	No action, continue treatment. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. If resolved, then continue with next dose scheduled.

[redacted]

Grade 3 (> 5.0 – 20.0 x ULN)	Recommendation: interrupt dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. If resolved, then continue with next dose scheduled.
Grade 4 (> 20.0 x ULN)	**Mandatory:** Permanently discontinue the patient from the study.
Combined elevations of ALT and bilirubin (direct conjugated)	
• For patients with normal baseline ALT and direct bilirubin value: ALT ≥ 3.0 x ULN combined with direct bilirubin ≥ 2.0 x ULN without evidence of cholestasis [c] OR • For patients with elevated baseline ALT or direct bilirubin value: ALT ≥ 2 x baseline AND ≥ 2.0 x baseline direct bilirubin	**Mandatory:** in the absence of cholestasis (alkaline phosphatase [ALP] < ULN), patient should be immediately discontinued from treatment. Repeat LFTs[b] as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.5.2.1 for additional follow-up evaluations as applicable.
Infections	
Grade 1 and 2	No action, continue treatment.
Grade 3	**Mandatory:** Interrupt dose until resolved. If resolved, then continue with next dose scheduled.
Grade 4	**Mandatory**: Permanently discontinue the patient from the study.
Infusion-related reactions (IRR)	
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Recommendation: • Continue study treatment and increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Consider slowing infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Recommendation: • Temporarily interrupt infusion and increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Administer appropriate medical therapy as per local institutional guidelines and clinical presentation. • Steroids should be used with caution unless clinically indicated (e.g. management of hypersensitivity /anaphylaxis) (Brandow et al, 2020). • If symptoms resolve, restart infusion per investigator discretion at a slower rate (e.g. 50%) under continuous observation. Ensure a minimum of 1 hour observation period prior to restarting the infusion.

[redacted]

	• Before restarting, administer premedication (e.g. analgesics such as paracetamol/acetaminophen or NSAIDs and anti-histamines within 1 hour prior to dosing) as per local institutional guidelines for prophylaxis of infusion related reactions, including subsequent infusions. • In case of recurring infusion related reactions despite premedication and prolonged infusion, discontinue study treatment.
Grade 3 and 4 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Life-threatening consequences; urgent intervention indicated	Mandatory: • Permanently discontinue study treatment and initiate appropriate medical care. • Collect blood sample immediately after onset of AE occurs for further characterization of the IRR (see section 6.5.2).

General Note: Decision for dosing is made on prior lab results, not those from labs performed on the day of infusion. If lab results found to be abnormal, repeat (unscheduled) labs should be performed at least 1 week prior to scheduled dose in order to have results to show resolution of the abnormality before the scheduled dose is given

[a] Toxicity Criteria for AEs (Common Terminology Criteria for AEs [CTCAE] Version 5.0)

[b] Core LFTs consist of ALT, aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), total bilirubin (fractionated [direct and indirect], lactate dehydrogenase (LDH), albumin, creatinine kinase and ALP

[c] "Cholestasis" defined as ALP elevation (> 2.0 x ULN and R value < 2). Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestasis (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R > 2 and < 5) liver injury

It is recommended that trial participants with confirmed active COVID-19 or presenting with symptoms indicative of COVID-19 such as fever, cough, difficulty breathing, sore throat or feeling unwell should interrupt crizanlizumab until the trial participant has fully recovered; in case of suspected COVID-19, testing for COVID-19 is recommended as per local guidance/practice. For confirmed patients, re-testing is advised before re-initiating study treatment to ensure adequate recovery. Patients with suspected infection tested negative may continue study treatment. In case of trial participants who have been exposed to someone infected by COVID-19 and is in self-quarantine, it is recommended that administration of crizanlizumab be delayed until the trial participant completes the quarantine and remains asymptomatic and/or COVID-19 has been ruled out.

6.5.1.2 Standard of care for chronic kidney disease due to sickle cell disease

Any of the following drugs that the patient is receiving at study entry will be considered the patient's standard of care: HU/HC, ACE inhibitors, and/or ARBs. Patient will continue to take their usual standard of care drug(s) during the study. Patients must have been receiving their standard of care drug(s) prior to study entry according to the dosing requirements in Table 6-1, and must plan to continue taking the drug(s) at the same dose and schedule until the patient has reached the end of the study. No dose modifications in standard of care medications may be

[redacted]

made during the study, except for dose modifications due to AEs or weight adjustments at the discretion of the physician. Starting any new treatment with HU/HC, within 6 months prior to screening and ACE inhibitors, or ARBs from within 3 months prior to screening up to the end of the study is prohibited and will be a protocol deviation (see Section 6.2.2). If a physician deems it medically necessary to terminate or alter standard of care treatment(s) during the study, changes should not lead by default to discontinuation of the patient from the trial (see Section 9.1); however, the Novartis medical monitor must be notified.

6.5.2 Follow-up for toxicities

In case of a grade 3 or 4 infusion-related reaction additional blood samples for cytokines and complement will be collected as outlined in Table 6-3. Collection of additional blood samples for cytokines and complement include but are not limited to IFNy, IL-1, IL-2, IL-6, TNFa, C3a, C5a, SC5b-9, as well as p-selectin and tryptase.

These blood samples should be collected immediately and no later than up to 1 hour post infusion.

Once the above sample is obtained immediately post infusion it is at the discretion of the investigator if additional follow up blood samples should be obtained.

Patients whose study treatment is interrupted or permanently discontinued due to an AE must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts (e.g., ophthalmologist, endocrinologist, dermatologist, psychiatrists) should be consulted as deemed necessary. All patients must be followed up for AEs and SAEs until the end of their safety follow-up period (ie. 30-day safety follow-up or 105-day follow-up [as applicable]).

6.5.2.1 Follow-up on potential drug-induced liver injury cases

Alanine aminotransferase increase combined with direct bilirubin increase may be indicative of potential drug-induced liver injury, and should be considered as clinically important events.

NOTE: Patients with SCD tend to have elevated transaminases, especially AST, and indirect bilirubin due to the hemolytic nature of this condition. Hence, ONLY ALT and direct bilirubin will be required in this criteria AST will NOT be considered.

Patients meeting the following criteria will require further follow-up as outlined below:

- **For patients with normal ALT and direct bilirubin value at baseline:** ALT ≥ 3.0 x ULN combined with direct bilirubin ≥ 2.0 x ULN OR international normalized ratio (INR) > 1.5 without evidence of cholestasis (no ALP elevation)
- **For patients with elevated baseline ALT or direct bilirubin value at baseline:** ALT ≥ 2 x baseline AND ≥ 2 x baseline direct bilirubin
- **For patients with normal ALT at baseline:** ALT ≥ 5.0 x ULN for more than 2 weeks
- **For patients with elevated ALT at baseline:** ALT ≥ 3.0 x baseline for more than 2 weeks

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2.

[redacted]

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions as described below:

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, LDH, prothrombin time (PT)/INR and ALP.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g., biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of crizanlizumab.
5. Additional testing for other hepatotropic viral infection (cytomegalovirus, Epstein-Barr virus or herpes simplex virus), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, and thus, meet the definition of SAE and should be reported as SAE using the term “potential drug-induced liver injury.” All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Crizanlizumab compliance will be assessed by administration of the crizanlizumab under the supervision of the investigator or his/her designee and will be verified by determinations of crizanlizumab in serum. This information must be captured in the source document and in the Drug Accountability Form.

Regarding standard of care compliance, the investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient’s safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the patient. This information should be captured in the source document at each visit.

6.7 Preparation and dispensation

Each study site will be supplied with crizanlizumab in packaging as described in Section 6.1.1. A unique medication number is printed on the crizanlizumab label.

[redacted]

Investigator staff will identify the drug kits to dispense to the patient by contacting the IRT and obtaining the medication number(s). The drug has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Crizanlizumab solution will be prepared by a pharmacist or study personnel appropriately trained in the preparation of solutions for parenteral administration in accordance with the Pharmacy Manual.

Patients should be closely observed for potential IRRs including rigors, chills, wheezing, flushing, pruritus, rash, hypotension, hypoxemia, and fever, and vital signs monitored more frequently if clinically indicated, in accordance with the Pharmacy Manual. The same applies for the subsequent infusions, if medically indicated. If a patient experiences an IRR, he/she may receive pre-medication on subsequent dosing days as per institutional standard of care, at the discretion of the treating physician.

If a patient experiences a Grade 3 or 4 IRR, the patient will discontinue crizanlizumab. Please refer to Table 6-3 for further guidance on management of IRRs.

Standard of care medications will be prepared and dispensed according to the instructions specified on the labels and in the prescribing information, and in accordance with local standard practice.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Crizanlizumab must be received by the pharmacist or delegate at the study site, handled and stored safely and properly, and kept in a secured location. Upon receipt, all of the drug must be stored according to the instructions specified on the labels and in the IB. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

The pharmacist or delegate will inventory and acknowledge receipt of all shipments of crizanlizumab. The pharmacist will also keep accurate records of the quantities of crizanlizumab dispensed and used by each patient. Monitoring of crizanlizumab will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the crizanlizumab but no information about the patient except for the medication number.

At the conclusion of the study, and as appropriate during the course of the study, the investigator or delegate will destroy all unused crizanlizumab, packaging, drug labels as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

Investigators will instruct patients to store and take their standard of care medications according to the instructions specified on the labels and in the prescribing information. Patients should bring their standard of care medications to study visits for reconciliation of medications used. The investigator will keep accurate records of quantities of standard of care medications used by each patient. A monitor will ensure accountability of all standard of care medications used.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

All kits of crizanlizumab assigned by the IRT will be recorded in the IRT system.

7 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her level of understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed ICF that complies with the International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements for the duration of the study. If there is any question that the patient will not reliably comply, then they should not be entered in the study.

The study includes an optional DNA component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents

this option to the patient, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent. Declining to participate in these optional assessments will in no way affect the patient's ability to join the main research study. Refer to Section 8.5.3 for additional details on these assessments.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Patients might be asked to complete optional questionnaires to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The assessment schedule lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Screening assessments can occur within 28 days prior to Week 1 Day 1 (IRT enrollment) as per Table 8-1. There is a ± 3-day visit window permitted on dosing and assessments to take into account scheduling over public holidays on Week 3 Day 1, a ± 7-day visit window from Week 7 Day 1 to Week 51 Day 1, a ± 3-day visit window on Week 53 Day 1, ± 5-day visit window for the 30-day safety follow-up visit, + 7-day visit window for the 105-day follow-up (as applicable), and ± 7 day visit window for the Week 53 urine ACR/PCR assessment (for patients who discontinue treatment early). Upon completion of the Week 53 Day 1 visit, the investigator will complete the EOT Disposition eCRF. Patients who discontinue study treatment early should not be considered withdrawn from the study unless they withdraw their consent (Section 9.1.1). Missed or rescheduled visits should not lead to automatic discontinuation. Patients who discontinue study treatment early should be scheduled for a visit as soon as possible (within 7 days of the last dose of the discontinued study treatment), at which time all of the assessments listed for visit EOT will be performed. Patients who discontinue treatment early will also return for a Week 53 urine ACR/PCR assessment. The Week 53 urine ACR/PCR assessment should occur 12 months after the first dose of study treatment.

Patients who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed.

All patients will be followed in the mandatory safety follow-up period, which includes safety assessments at 30 days (phone call) and 105 days (study visit, as applicable) after the Week 51 Day 1 visit, or if the patient discontinued the study early, the last dose of discontinued study treatment. Patients who will receive crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105 day follow-up. The end of the safety follow-up period for these patients will be the 30-day follow-up. All other patients are required to complete the 105-day follow-up.

Table 8-1 Assessment Schedule

Period	Screening	Treatment															End of Treatment (EOT)	Follow-up		
Visit Name	Screening	Week 1 Day 1	Week 3 Day 1	Week 7 Day 1	Week 11 Day 1	Week 15 Day 1	Week 19 Day 1	Week 23 Day 1	Week 27 Day 1	Week 31 Day 1	Week 35 Day 1	Week 39 Day 1	Week 43 Day 1	Week 47 Day 1	Week 51 Day 1	Week 53 Day 1[1]	EOT[2]	30-day Follow-up phone call	105-day Follow-up	Week 53 urine ACR/PCR assessment [20] (for patients who discontinue treatment early)
Visit Numbers[3]	1	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	199	201	202	299
Days	-28 to -1	1	15 ± 3	43 ± 7	71 ± 7	99 ± 7	127 ± 7	155 ± 7	183 ± 7	211 ± 7	239 ± 7	267 ± 7	295 ± 7	323 ± 7	351 ± 7	365 ± 3	Within 7 days of last dose	30-day Follow-up[4] ± 5	105-day Follow-up[4] + 7	365 ± 7
Informed consent	X																			
IRT randomization		X[5]																		
Disposition	X																X	X	X	
Demography	X																			
Inclusion/exclusion criteria	X																			
ECOG performance status	X	X[5]																		
Medical history/current medical conditions	X																			
Complications of SCD	X																			
Sickle cell VOC history	X																			
Alcohol history	X																			
Smoking history	X																			

[redacted]

Period	Screening	Treatment															End of Treatment (EOT)	Follow-up		
Visit Name	Screening	Week 1 Day 1	Week 3 Day 1	Week 7 Day 1	Week 11 Day 1	Week 15 Day 1	Week 19 Day 1	Week 23 Day 1	Week 27 Day 1	Week 31 Day 1	Week 35 Day 1	Week 39 Day 1	Week 43 Day 1	Week 47 Day 1	Week 51 Day 1	Week 53 Day 1[1]	EOT[2]	30-day Follow-up phone call	105-day Follow-up	Week 53 urine ACR/PCR assessment [20] (for patients who discontinue treatment early)
Visit Numbers[3]	1	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	199	201	202	299
Days	-28 to -1	1	15 ± 3	43 ± 7	71 ± 7	99 ± 7	127 ± 7	155 ± 7	183 ± 7	211 ± 7	239 ± 7	267 ± 7	295 ± 7	323 ± 7	351 ± 7	365 ± 3	Within 7 days of last dose	30-day Follow-up[4] ± 5	105-day Follow-up[4] + 7	365 ± 7
Hepatitis screen	X																			
HIV screen	X																			
Physical examination[16]	S																			
Abbreviated physical examination[5]		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S		S	
Vital signs[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Body height[6; 16]	X															X[6]	X[6]			
Body weight[5; 16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
BMI	X																			
Hematology[5]	X	X[7]	X		X	X			X			X				X	X			
Platelets (local)[21]	X	X	X		X	X			X			X				X	X			
Clinical chemistry[5]	X	X[7]	X		X	X			X			X				X	X			
Coagulation panel[5]	X	X[7]	X		X	X			X			X				X	X			
[redacted]																				

[redacted]

Period	Screening	Treatment															End of Treatment (EOT)	Follow-up		
Visit Name	**Screening**	**Week 1 Day 1**	**Week 3 Day 1**	**Week 7 Day 1**	**Week 11 Day 1**	**Week 15 Day 1**	**Week 19 Day 1**	**Week 23 Day 1**	**Week 27 Day 1**	**Week 31 Day 1**	**Week 35 Day 1**	**Week 39 Day 1**	**Week 43 Day 1**	**Week 47 Day 1**	**Week 51 Day 1**	**Week 53 Day 1[1]**	**EOT[2]**	**30-day Follow-up phone call**	**105-day Follow-up**	**Week 53 urine ACR/PCR assessment [20]** (for patients who discontinue treatment early)
Visit Numbers[3]	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**113**	**114**	**115**	**199**	**201**	**202**	**299**
Days	**-28 to -1**	**1**	**15 ± 3**	**43 ± 7**	**71 ± 7**	**99 ± 7**	**127 ± 7**	**155 ± 7**	**183 ± 7**	**211 ± 7**	**239 ± 7**	**267 ± 7**	**295 ± 7**	**323 ± 7**	**351 ± 7**	**365 ± 3**	**Within 7 days of last dose**	**30-day Follow-up[4] ± 5**	**105-day Follow-up[4] + 7**	**365 ± 7**
Cytokines, complement, tryptase, p-selectin[17]																				
Urinalysis (see Table 8-3 for tests to be assessed locally)[5]	X	X[7]				X			X			X				X	X			
Serum pregnancy test	X															X	X		X	
Urine pregnancy test (assessed locally)[5]		S	S	S	S	S	S	S	S	S	S	S	S	S	S					
[redacted]																				
Hemoglobin variants (Hb electrophoresis or HPLC)	X																			
Fetal hemoglobin (HbF)	X					X			X							X	X			

[redacted]

Period	Screening	Treatment															End of Treatment (EOT)	Follow-up		
Visit Name	**Screening**	**Week 1 Day 1**	**Week 3 Day 1**	**Week 7 Day 1**	**Week 11 Day 1**	**Week 15 Day 1**	**Week 19 Day 1**	**Week 23 Day 1**	**Week 27 Day 1**	**Week 31 Day 1**	**Week 35 Day 1**	**Week 39 Day 1**	**Week 43 Day 1**	**Week 47 Day 1**	**Week 51 Day 1**	**Week 53 Day 1[1]**	**EOT[2]**	**30-day Follow-up phone call**	**105-day Follow-up**	**Week 53 urine ACR/PCR assessment [20]** (for patients who discontinue treatment early)
Visit Numbers[3]	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**113**	**114**	**115**	**199**	**201**	**202**	**299**
Days	**-28 to -1**	**1**	**15 ± 3**	**43 ± 7**	**71 ± 7**	**99 ± 7**	**127 ± 7**	**155 ± 7**	**183 ± 7**	**211 ± 7**	**239 ± 7**	**267 ± 7**	**295 ± 7**	**323 ± 7**	**351 ± 7**	**365 ± 3**	**Within 7 days of last dose**	**30-day Follow-up[4] ± 5**	**105-day Follow-up[4] + 7**	**365 ± 7**
Optional DNA collection		X (once any time during the study)																		
Sickle cell – AKI event	X	Continuous																		
Sickle cell – VOC event[8]	X	Continuous																		
Chest X-ray	X[9]	If clinically indicated																	If clinically indicated	
Healthcare resource utilization due to AKI, VOCs and/or other SCD complications[10]	X	Continuous																		
Missed school or work due to AKI, VOCs and/or other SCD complications[10]	X	Continuous																		

[redacted]

Period	**Screening**	**Treatment**															**End of Treatment (EOT)**	**Follow-up**		
Visit Name	**Screening**	**Week 1 Day 1**	**Week 3 Day 1**	**Week 7 Day 1**	**Week 11 Day 1**	**Week 15 Day 1**	**Week 19 Day 1**	**Week 23 Day 1**	**Week 27 Day 1**	**Week 31 Day 1**	**Week 35 Day 1**	**Week 39 Day 1**	**Week 43 Day 1**	**Week 47 Day 1**	**Week 51 Day 1**	**Week 53 Day 1[1]**	**EOT[2]**	**30-day Follow-up phone call**	**105-day Follow-up**	**Week 53 urine ACR/PCR assessment [20]** (for patients who discontinue treatment early)
Visit Numbers[3]	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**113**	**114**	**115**	**199**	**201**	**202**	**299**
Days	**-28 to -1**	**1**	**15 ± 3**	**43 ± 7**	**71 ± 7**	**99 ± 7**	**127 ± 7**	**155 ± 7**	**183 ± 7**	**211 ± 7**	**239 ± 7**	**267 ± 7**	**295 ± 7**	**323 ± 7**	**351 ± 7**	**365 ± 3**	**Within 7 days of last dose**	**30-day Follow-up[4] ± 5**	**105-day Follow-up[4] + 7**	**365 ± 7**
Prior/concomitant medications[10]	X	Continuous																		
Prior/concomitant medications – Analgesic[10]	X	Continuous																		
Prior/concomitant medications – ESA[10]	X	Continuous																		
Prior/concomitant medications – HA approved form(s) of L-glutamine[10]	X	Continuous																		
Concomitant non-drug therapies/procedures[10]	X	Continuous																		
Incidence of transfusion[10]	X	Continuous																		

[redacted]

Period	Screening	Treatment															End of Treatment (EOT)	Follow-up		
Visit Name	Screening	Week 1 Day 1	Week 3 Day 1	Week 7 Day 1	Week 11 Day 1	Week 15 Day 1	Week 19 Day 1	Week 23 Day 1	Week 27 Day 1	Week 31 Day 1	Week 35 Day 1	Week 39 Day 1	Week 43 Day 1	Week 47 Day 1	Week 51 Day 1	Week 53 Day 1[1]	EOT[2]	30-day Follow-up phone call	105-day Follow-up	Week 53 urine ACR/PCR assessment [20] (for patients who discontinue treatment early)
Visit Numbers[3]	1	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	199	201	202	299
Days	-28 to -1	1	15 ± 3	43 ± 7	71 ± 7	99 ± 7	127 ± 7	155 ± 7	183 ± 7	211 ± 7	239 ± 7	267 ± 7	295 ± 7	323 ± 7	351 ± 7	365 ± 3	Within 7 days of last dose	30-day Follow-up[4] ± 5	105-day Follow-up[4] + 7	365 ± 7
12-lead ECG	X	If clinically indicated														X	X		If clinically indicated	
[redacted]																				
AEs/SAEs	X	Continuous																		
IRR[19]		Continuous																		
Urine ACR[5,11,]	X	X				X			X			X				X	X			X
Urine PCR[5,11]		X							X							X	X			X
eGFR[5,12]	X[12]	X				X			X			X				X	X			
Immunogenicity[5,13] (see also Table 8-6)		X	X		X			X				X				X	X		X	
PK[5,13] (see also Table 8-6)		X	X		X			X				X				X	X		X	
[redacted]																				

[redacted]

Period	Screening	Treatment															End of Treatment (EOT)	Follow-up		
Visit Name	Screening	Week 1 Day 1	Week 3 Day 1	Week 7 Day 1	Week 11 Day 1	Week 15 Day 1	Week 19 Day 1	Week 23 Day 1	Week 27 Day 1	Week 31 Day 1	Week 35 Day 1	Week 39 Day 1	Week 43 Day 1	Week 47 Day 1	Week 51 Day 1	Week 53 Day 1[1]	EOT[2]	30-day Follow-up phone call	105-day Follow-up	Week 53 urine ACR/PCR assessment [20] (for patients who discontinue treatment early)
Visit Numbers[3]	1	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	199	201	202	299
Days	-28 to -1	1	15 ± 3	43 ± 7	71 ± 7	99 ± 7	127 ± 7	155 ± 7	183 ± 7	211 ± 7	239 ± 7	267 ± 7	295 ± 7	323 ± 7	351 ± 7	365 ± 3	Within 7 days of last dose	30-day Follow-up[4] ± 5	105-day Follow-up[4] + 7	365 ± 7
Standard of care – HU/HC[14]	X	Administered as clinically indicated																		
Standard of care – ACE inhibitors[14]	X	Administered as clinically indicated																		
Standard of care – ARBs[14]	X	Administered as clinically indicated																		
Crizanlizumab administration[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X					

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Upon completion of the Week 53 Day 1 visit, the investigator will complete the EOT Disposition eCRF
[2] Visit "EOT" is only for patients for whom the decision is made to discontinue the patient from the study early prior to visit Week 51 Day 1
[3] Visit structure given for internal programming purpose only
[4] The 30 day follow up phone call and 105 day follow up visit are relative to the Week 51 Day 1 visit, or if discontinued study treatment early, the last dose of the discontinued study treatment. Patients who will receive crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105 day follow-up. The end of the safety follow-up period for these patients will be the 30-day follow-up. All other patients are required to complete the 105-day follow-up.

[redacted]

[6] At Week 53 Day 1 or visit EOT, height will only be assessed in patients aged 16 or 17 years

[redacted]

Period	Screening	Treatment															End of Treatment (EOT)	Follow-up		
Visit Name	Screening	Week 1 Day 1	Week 3 Day 1	Week 7 Day 1	Week 11 Day 1	Week 15 Day 1	Week 19 Day 1	Week 23 Day 1	Week 27 Day 1	Week 31 Day 1	Week 35 Day 1	Week 39 Day 1	Week 43 Day 1	Week 47 Day 1	Week 51 Day 1	Week 53 Day 1[1]	EOT[2]	30-day Follow-up phone call	105-day Follow-up	Week 53 urine ACR/PCR assessment [20] (for patients who discontinue treatment early)
Visit Numbers[3]	1	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	199	201	202	299
Days	-28 to -1	1	15 ± 3	43 ± 7	71 ± 7	99 ± 7	127 ± 7	155 ± 7	183 ± 7	211 ± 7	239 ± 7	267 ± 7	295 ± 7	323 ± 7	351 ± 7	365 ± 3	Within 7 days of last dose	30-day Follow-up[4] ± 5	105-day Follow-up[4] + 7	365 ± 7

[7] Not to be repeated on Day 1 if screening assessment took place within 72 hours
[8] Other acute pain crisis managed at home will also be collected
[9] Within 3 months prior to Week 1 Day 1
[10] Parameter refers to data to be collected (i.e., if any healthcare resource utilization or concomitant medication administration or procedure, etc, occurred). See also Table 8-8
[11] Three urine samples will be collected for each visit time point for which ACR and/or PCR are to be assessed. See Section 8.3.1 and Section 8.3.2 for further details
[12] Any available eGFR data for the 2-year period prior to screening will be collected
[13] Immunogenicity and PK assessments are not required for patients randomized to the standard of care alone arm
[14] Recording standard of care drugs: Any of the following drugs being taken at study entry will be considered the patient's standard of care: HU/HC, ACE inhibitors, and/or ARBs. No dose modifications in standard of care medications may be made during the study, except for dose modifications due to AEs or weight adjustments at the discretion of the physician. Any dose modifications made to the patient's standard of care drug(s) during the study will be recorded
[15] Only patients randomized to the crizanlizumab + standard of care arm. Refer to Section 6.5.1.1 for instructions in case of crizanlizumab dose delay.
[16] See Table 8-2 for details

[redacted]

[redacted]

Period	Screening	Treatment															End of Treatment (EOT)	Follow-up		
Visit Name	Screening	Week 1 Day 1	Week 3 Day 1	Week 7 Day 1	Week 11 Day 1	Week 15 Day 1	Week 19 Day 1	Week 23 Day 1	Week 27 Day 1	Week 31 Day 1	Week 35 Day 1	Week 39 Day 1	Week 43 Day 1	Week 47 Day 1	Week 51 Day 1	Week 53 Day 1[1]	EOT[2]	30-day Follow-up phone call	105-day Follow-up	Week 53 urine ACR/PCR assessment [20] (for patients who discontinue treatment early)
Visit Numbers[3]	1	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	199	201	202	299
Days	-28 to -1	1	15 ± 3	43 ± 7	71 ± 7	99 ± 7	127 ± 7	155 ± 7	183 ± 7	211 ± 7	239 ± 7	267 ± 7	295 ± 7	323 ± 7	351 ± 7	365 ± 3	Within 7 days of last dose	30-day Follow-up[4] ± 5	105-day Follow-up[4] + 7	365 ± 7

[19] Certain adverse events reported in the AE/SAE eCRF as Infusion Related Reactions will require the IRR eCRF to be completed. Refer to the CRF completion guidelines (CCGs) for further information.

[20] Patients who discontinue treatment early will return for a Week 53 urine ACR/PCR assessment. The Week 53 urine ACR/PCR assessment should occur 12 months after the first dose of study treatment. The Week 53 urine ACR/PCR visit may fall before or after the safety follow-up visits depending on the patient's last dose of study treatment.

[21] Local sampling for platelet assessment will also be performed throughout the trial for adults and adolescents with body weight >45kg

[redacted]

8.1 Screening

After signing the study ICF, the screening assessments will be done within 1 to 28 days prior to baseline (Week 1 Day 1) (see Table 8-1) for list of assessments to be performed. The investigator will obtain consent/assent of patients and/or parents according to local procedures. Rescreening of patients is allowed once per patient per protocol version (ie. a patient can be re-screened under an amended protocol based on the changes in inclusion/exclusion criteria across versions). The investigator has the discretion to include/exclude a patient in the study, who will be found to have symptoms representative of COVID-19 or tested positive for COVID-19 during the screening phase. Should the investigator choose to screen fail the patient based on symptoms or positive COVID-19 test, the patient can be re-screened more than once. In this case a new Patient Number will be assigned to the patient and the patient will be identified with this new number for the rest of his/her participation in the study. If patient has been enrolled and treated, re-screening of patient is not allowed. In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria. A new ICF must be signed only if there is an interruption in the patient's eligibility evaluation and the investigator chooses to re-screen the patient following screen failure. If a new ICF is signed, AEs and medical history will be assessed relative to the new informed consent date.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range before screen failing the patient. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. For details of assessments, see Table 8-1 and Section 8.4.1.

8.1.1 Eligibility screening

The investigator is responsible to ensure only patients who meet all inclusion and none of the exclusion criteria are included in this study.

Following registration in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Patients who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during the screening phase (see SAE section for reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

[redacted]

Patients who are randomized and fail to start treatment, e.g., patients randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Patient demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the eCRF.

Patient demographic and baseline characteristic data to be collected on all patients include age, sex, self-identified race, and ethnicity. Patient race /ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Background medical information, including sickle cell history, SCD genotype, coinheritance of alpha thalassemia, % HbF, ECG, relevant and current medical history, ECOG performance status, as well has history of alcohol and smoking will be recorded. Any available eGFR data for the 2-year period prior to screening will be collected.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant therapy for further details on what information must be recorded on the appropriate eCRF.

Healthcare resource utilization history including patient disease burden, as assessed by the following, will also be recorded:

1. Sickle cell VOC history, including the number of:
    a. VOCs at home (not requiring healthcare resource utilization) in the previous 12 months
    b. VOCs requiring healthcare resource utilization in the previous 12 months, including the number of:
        - Hospitalizations in the 12 months
        - ER visits in the previous 12 months
    c. SCD complications other than VOCs requiring healthcare resource utilization in the previous 12 months, including the number of:
        - Hospitalizations in the 12 months
        - ER visits in the previous 12 months
2. Data will be collected for complicated and uncomplicated VOCs. Complicated VOCs are defined as ACS, hepatic sequestration, splenic sequestration, and priapism
3. Number of missed school days or work days due to VOCs and/or other SCD complications in the previous 12 months. Data will be collected for complicated and uncomplicated VOCs
4. Other complications of SCD, including, but not limited to, stroke, leg ulcers, asthma, avascular necrosis, pulmonary hypertension, retinopathy, other (investigator to specify)

[redacted]

Other baseline characteristics and assessments, including ACR, PCR, and eGFR, are detailed in Table 8-1.

8.3 Efficacy

Samples for the assessment of albuminuria (urine ACR), urine PCR, eGFR, and progression of CKD will be collected at the time points indicated in Table 8-1. These assessments are described below and further details regarding the collection, storage, shipment, and analysis of these samples are provided in the laboratory manual.

Note that patients who discontinue study treatment early should not be considered withdrawn from the study unless they withdraw their consent (Section 9.1.1). A Week 53 urine ACR/PCR assessment is required for patients who discontinue study treatment early.

8.3.1 Urine albumin to creatinine ratio

Three urine samples will be collected for each visit time point for which albumin and creatinine concentrations are to be assessed for ACR (these will be the same samples that are assessed for PCR, as applicable (see Section 8.3.2)). Two of the three samples should be collected as morning voids. Morning void samples can be collected at any time during the screening and study visit windows on two consecutive days (refer to laboratory manual for sample stability requirements). The sample collected during the study visit can be collected either prior to, on or after the day of the morning sample collections. The average of the 3 samples (2 morning void samples and 1 sample collected during the visit) will be used to determine patient eligibility. The samples will be obtained midstream and will be stored as defined in the laboratory manual.

As noted above (Section 8.3), patients who discontinue study treatment early will return for a Week 53 urine ACR/PCR assessment as indicated in Table 8-1.

Albumin and creatinine concentrations will be measured by the central laboratory using an immunological assay capable of specifically and precisely quantifying albumin at low concentrations and of producing quantitative results over the clinically relevant range. Albumin concentrations will be reported as a ratio to urinary creatinine concentration (mg/g) for each of the three samples. The ACR results will be expressed to whole numbers. Further details will be provided in the laboratory manual.

It is important to collect all 3 urine samples and that 2 of the samples are morning voids at all collection time points to help minimize the variability in ACR measurements.

8.3.2 Urine protein to creatinine ratio

Three urine samples will be collected for each visit time point for which protein and creatinine concentrations are to be assessed for PCR (these will be the same samples that are assessed for ACR (see Section 8.3.1)). Two of the three samples should be collected as morning voids. Morning void samples should be collected during the study visit window on two consecutive days (refer to laboratory manual for sample stability requirements). The sample collected during the study visit can be collected either prior to, on or after the day of the morning sample

[redacted]

collections. PCR is not required for eligibility and will be assessed starting W1D1 and subsequent timepoints. The samples will be obtained midstream and will be stored as defined in the laboratory manual.

As noted above (Section 8.3), patients who discontinue study treatment early will return for a Week 53 urine ACR/PCR assessment as indicated in Table 8-1.

Protein and creatinine concentrations will be assessed by the central laboratory. Protein concentrations will be reported as a ratio to urinary creatinine concentration (mg/g) for each of the three samples. The PCR results will be expressed to whole numbers. Further details will be provided in the laboratory manual.

8.3.3 Estimated glomerular filtration rate

The eGFR will be calculated in the serum from the blood samples collected for assessment of clinical chemistry parameters. eGFR will be assessed by the central laboratory, as specified in the laboratory manual.

The central laboratory will calculate eGFR using the 2009 CKD-EPI formula for patients ≥ 18 at screening and 2009 Creatinine-based "Bedside Schwartz" equation for patients < 18 at screening. While on the study, the patient's eGFR will continue to be calculated by the same formula used at screening.

2009 CKD-EPI formula

The CKD-EPI formula (Levey et al 2009), without the correction for race, to be used in this study for patients ≥ 18 at screening to estimate GFR is as follows:

$141 \times \min(Scr/k, 1)^{\alpha} \times \max(Scr/k, 1)^{-1.209} \times 0.993^{Age}$

[× 1.018 if female], where:

- Scr is serum creatinine (in mg/dL)
- k is 0.7 for females and 0.9 for males
- α is -0.329 for females and -0.411 for males
- min is the minimum of Scr/k or 1
- max is the maximum of Scr/k or 1

2009 Creatinine-based "Bedside Schwartz" equation

The 2009 Creatinine-based "Bedside Schwartz" equation will be used in this study to estimate eGFR for patients < 18 at screening (Schwartz et al 2009). The equation is as follows:

eGFR =

0.413 x (height/Scr) if height is expressed in centimeters

OR

41.3 x (height/Scr) if height is expressed in meters

[redacted]

8.3.4 Progression of chronic kidney disease

The progression of CKD will be assessed based on the blood samples collected for the assessment of eGFR (Section 8.3.3). The progression of CKD, which is based on both eGFR and ACR, will be assessed according to the classification presented in Figure 8-1 (based on KDIGO 2013). Specifically, CKD progression will be defined as follows:

- Increase in CKD progression category: i.e., Category 1 to ≥ 2; Category 2 to ≥ 3; or Category 3 to 4 (see Figure 8-1)
- Accompanied by a 25% or greater drop in eGFR from baseline
- Decline in eGFR category:

Grade 1 (normal or high), eGFR ≥ 90 mL/min/1.73m^2

Grade 2 (mildly decreased), eGFR 60-89 mL/min/1.73m^2

Grade 3a (mildly to moderately decreased), eGFR 45-59 mL/min/1.73m^2

Grade 3b (moderately to severely decreased), eGFR 30-44 mL/min/1.73m^2

Grade 4 (severely decreased), eGFR 15-29 mL/min/1.73m^2

Grade 5 (kidney failure), eGFR < 15 mL/min/1.73m^2

A certain drop in eGFR is defined as a drop in eGFR category accompanied by a 25% or greater drop in eGFR from baseline

- Rapid progression is defined as a sustained decline in eGFR of more than 5 mL/min/1.73 m^2/year
- The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up

A 50% increase in ACR for patients with severe (A3) albuminuria and a doubling of albumin levels in patients with moderate (A2) albuminuria. Predictors of progression include both the level of albuminuria and the level of GFR.

[redacted]

Figure 8-1 Glomerular filtration rate and albuminuria grid to reflect the risk of chronic kidney disease progression

GFR categories (mL/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mmol
	G1	Normal or high	≥ 90	0	1	2
	G2	Mildly decreased	60-89	0	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4
	G5	Kidney failure	< 15	4	4	4

Glomerular filtration rate and albuminuria grid to reflect the risk of progression (where CKD progression category 0 is the lowest risk of progression and 4 is the highest risk)
[1] CKD progression categories according to KDIGO (2013); patients in this study will have eGFR ≥ 45 to ≤140 mL/min/1.73 m² and ACR of ≥ 100 to < 2000 mg/g (i.e., CKD progression categories 1, 2, or 3). Assessment should be based on ACR in mg/g.

8.3.5 Appropriateness of efficacy assessments

The primary endpoint of this study is the proportion of patients with ≥ 30% decrease in ACR at 12 months from baseline.

Based on the recommendation of a consensus panel focused on SCD end organ considerations specifically evaluating renal endpoints in SCD trials, albuminuria was recommended as a potential endpoint. The outcome measure suggested that was deemed clinically relevant was a 30% decrease in albuminuria evaluated by ACR (Farrell et al 2019). A meta-analysis of clinical trial data also suggests that each 30% decrease in geometric mean albuminuria by the treatment relative to the control was associated with an average 27% lower hazard for the clinical endpoint. This association strengthened after restricting analyses to patients with baseline albuminuria of more than 30 mg/g. The model from this analysis predicted that treatments that decrease the geometric mean albuminuria relative to the control group by 30% would have a high likelihood to confer clinical benefit (Heerspink et al 2019).

[redacted]

The meta-analysis was based on 41 eligible treatment comparisons from randomized studies that provided sufficient patient level data on 29979 participants (71% of whom had diabetes). Eligible participants were aged ≥ 18 years with an eGFR of ≥ 15 mL/min/1.73 m^2, quantifiable measurements of albuminuria or proteinuria at baseline and within 12 months of follow up, and information on the incidence of end stage kidney disease. The primary objective of the meta-analysis was to assess the validity of change in albuminuria as a surrogate endpoint for progression of CKD by modelling the association between treatment effects on 6-month change in urine ACR, and treatment effects on the composite clinical endpoint across the studies. The clinical endpoint (defined as a composite of treated end stage kidney disease, eGFR of < 15 mL/min/1.73 m^2, or doubling of serum creatinine sustained at the subsequent visit) was reached in 13% participants over a median follow up of 3.4 years (Heerspink et al 2019).

Microalbuminuria is one of the earliest signs of glomerular injury in patients with SCD, albuminuria in the early stages of CKD appears to be a sensitive marker of CKD progression, and an early decrease in albuminuria is considered to be indicative of a favorable response to treatment (Bartolucci et al 2016, Heerspink et al 2019). In a study of 1513 patients with Type 2 diabetes and nephropathy, the most rapid change (decrease) in the level of proteinuria (assessed by ACR) occurred within the first 3 to 6 months of treatment with an ARB, and over the next 6 months the decreases in proteinuria were much smaller, suggesting a stabilization of the effect of this ARB after 6 months (Brenner et al 2001).

Thus, the proportion of patients with ≥ 30% decrease in ACR at 12 months was selected as the primary variable in this study. To increase the precision of the treatment effect, it is planned to collect three ACR samples at each time point to calculate the mean. It is anticipated that standard of care medications in particular HU/HC may also have the most marked effect on proteinuria within the first 6 months. Therefore, the current study will require that patients have been taking a stable dose of their standard of care medications. Patients must have been on a stable dose of HU/HC, and ACE and/or ARB for at least 3 months prior to study entry. In addition, any patients receiving HA approved form(s) of L-glutamine as a concomitant medication, must have been on a stable dose for at least 6 months prior to study entry and plan to continue taking a stable dose throughout the study as it is not known how L-glutamine may affect ACR values.

The mean change in ACR from baseline to 3, 6, 9, and 12 months of treatment will be assessed as a secondary endpoint. An early decrease in albuminuria is considered to be indicative of a favorable response to treatment (Heerspink et al 2019) and the proportion of patients with ≥ 30% decrease in ACR at 6 months will be assessed as a secondary endpoint, as will the slope of ACR decline from baseline to 12 months based on ACR values at baseline and at 3, 6, 9, and 12 months.

Proteinuria has a role in the pathogenesis of CKD disease progression (KDIGO 2013). The KDIGO guidelines suggest that the two most preferred methods for initial testing of proteinuria comprise measuring urine ACRs or urine PCRs. As noted above, the primary endpoint of this study will be based on ACR. PCR will be assessed as a secondary endpoint: The proportion of patients with PCR improvement and stable PCR (improvement: ≥ 20% decrease in PCR from

[redacted]

baseline; stable: within ± 20% change from baseline) at 12 months compared to baseline (the 20% threshold in this endpoint is based on expert assessment of clinically meaningful improvements).

An important secondary endpoint of this study is the percentage change in eGFR from baseline to 3, 6, 9, and 12 months of treatment with crizanlizumab + standard of care compared to standard of care alone. The US FDA have stated that they anticipate that eGFR could be an appropriate surrogate endpoint for use as an efficacy clinical trial endpoint in adult patients with CKD secondary to multiple etiologies (Levey et al 2014).

As GFR cannot be measured directly, it may be estimated from the serum levels of endogenous filtration markers such as creatinine. The participants of a scientific workshop sponsored by the National Kidney Foundation and US FDA in 2012 agreed that an eGFR decline of 30% could be a valid and useful surrogate endpoint for progression to kidney failure in clinical trials of CKD, but the evidence was stronger for an eGFR decline of 40%, based on a follow-up duration of ≥ 2 to 3 years (Levey et al 2014). The patients to be included in the current study comprise SCD patients with CKD who are expected to be rapid decliners (see Section 5), despite having received standard of care for ≥ 6 months. Rapid decline can be defined as an annual rate of decline in eGFR of ≥ 3-5 mL/min/1.73 m^2 (Tsai et al 2017). There has been much debate regarding the best method to estimate GFR. The CKD-EPI formula has been selected for use in this study for patients ≥ 18 at screening; it matches the accuracy of the MDRD equation at GFR < 60 mL/min/1.73 m^2 and offers greater accuracy at higher GFRs (Florkowski and Chew-Harris 2011). The "Bedside Schwartz" formula will be used for patients <18 at screening. This formula was noted to be the most accurate formula to avoid overestimation of eGFR in children (Schwartz et al 2009). Nonetheless, challenges remain regarding the accurate assessment of eGFR across the full range of eGFRs anticipated in this study. Though this study will enroll patients considered rapid decliners based on both the level of albuminuria and eGFR, a study of longer duration, and a larger sample size would likely be required, thus it was thus decided to have an eGFR-based secondary endpoint for this study, rather than an eGFR primary endpoint.

The proportion of patients with CKD progression (based on both ACR and eGFR) from baseline to 12 months will also provide a clinically relevant assessment of a potential benefit with crizanlizumab + standard of care and standard of care alone.

8.4 Safety

Safety assessments will consist of monitoring and recording all AEs, based on CTCAE v5.0. It will also include regular monitoring of laboratory assessments including hematology, clinical chemistry, complement, cytokines and urinalysis (see Section 8.4.1), measurement of vital signs and physical examination (see Table 8-2), and ECG evaluation (see Section 8.4.2).

The assessment schedule details when each assessment is to be performed (Table 8-1).

For details on AE collection and reporting, refer to Section 10.1.1.

[redacted]

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination will be performed at screening. An abbreviated (short) physical exam will include the examination of general appearance and vital signs (blood pressure [systolic blood pressure and diastolic blood pressure] and pulse), as well as additional components of the physical exam (e.g., lower extremity examination), as needed based on observed signs or reported symptoms. A short physical exam will be at all visits starting from the Week 1 Day 1 visit. Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be recorded in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected) based on an average of 3 measurements, pulse measurement, respiratory rate, and body temperature. Vital signs will be assessed at each visit.
Height, weight and BMI	Height in centimeters (cm) will be measured at screening (all patients); then at the Week 53 Day 1 visit or visit EOT (only patients aged 16 or 17 years). Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at every visit up to the Week 53 Day 1 visit or visit EOT. BMI will be assessed at screening for eligibility.

8.4.1 Laboratory evaluations

Clinical laboratory analyses (hematology, clinical chemistry, urinalysis, coagulation, cytokines, complement, hepatitis and HIV markers, and serum pregnancy test) are to be performed centrally, unless otherwise mentioned in the schedule of assessments.

Novartis must be provided with a copy of the central laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well.

The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance. Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used (except in the event the results from the central laboratory are not yet

available or are partial at time of the first infusion, then eligibility may be based on the results from the local laboratory. In such a case, the results of the local laboratory will need to be recorded in the eCRF unscheduled pages and copy of the local lab normal ranges must be provided). Local laboratory values for ACR and eGFR results should not be used to confirm eligibility. Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) AE or when the treating physician cannot wait for central laboratory results for decision making. In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis. The results of the local laboratory will be recorded in the eCRF unscheduled pages if any the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available, or
- Local lab results document an AE not reported by the central lab, or
- Local lab results document an AE where the severity is worse than the one reported by the central lab, or
- Eligibility had to be based on the local lab results due to pending/missing central lab results.

Laboratory assessments (e.g. blood, urine) can be repeated during the screening period as deemed appropriate by the investigator.

At any time during the study up to safety follow-up, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. The severity of laboratory data will be graded using the CTCAE v5.0. Additional analyses are left to the discretion of the investigator.

Specifically, for platelet count, local sampling will also be performed throughout the trial for adults and adolescents with body weight > 45kg. To mitigate the potential for unevaluable or false LPTs, it is recommended to run blood samples as soon as possible. Based on in vitro data, platelet clumping was observed in some donor samples as early as 4 hours following the addition of crizanlizumab. When needed, manual platelet estimation via blood smear to assess adequacy of the platelet count may be considered. Additional details on the measures to be used will be provided in the laboratory manual.

The laboratory assessments are summarized in Table 8-3. Refer to the laboratory manual for further details of the laboratory evaluations to be performed in this study.

Table 8-3 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hb, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), mean corpuscular volume (MCV), Platelets*, Reticulocytes (%), RBCs, White blood cells, RBC Morphology, ANC, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other) (absolute value preferred, % are acceptable)
Clinical chemistry	eGFR (see Section 8.3.3 and Section 8.3.4) Albumin, ALP, ALT, AST, GGT, LDH, Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, BUN or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting)
Urinalysis	ACR (see Section 8.3.1) PCR (see Section 8.3.2) Albumin, protein, creatinine concentrations Macroscopic Panel (Dipstick) will be done locally: Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen Microscopic Panel: RBCs, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells performed, if a positive dipstick result
Coagulation	Prothrombin time (PT), INR, Activated partial thromboplastin time (APTT)
Cytokines/complement (including but not limited to) and additional tests	IFNy, IL-1, IL-2, IL-6, TNFa, C3a, C5a, SC5b-9, as well as p-selectin and tryptase (to be collected pre-infusion and up to 1hr - post-infusion at Week 1 Day 1, Week 3 Day 1 and Week 15 Day 1) and immediately after a grade 3 or 4 IRR for patient treated with crizanlizumab.
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-Polymerase Chain Reaction, HCV Ab (at screening only)
Additional tests	HIV Ab and RNA test (for viral load) (at screening only), Hb variants (at screening only) (see Section 8.4.1.1)
Pregnancy Test	For all women: serum pregnancy text (at screening, Week 53 Day 1, visit EOT, and follow-up visit), Urine pregnancy test at all other visits. See Section 8.4.4 for further details

* Local sampling for platelet counts will also be performed throughout the trial for adults and adolescents with body weight >45kg

8.4.1.1 Hemoglobin variants

Hemoglobin electrophoresis or HPLC will be used to screen for Hb variants in whole blood, including HbA, HbS, HbC, and HbA2. Fetal Hb (HbF) will be assessed at the time points defined in Table 8-1. Hb electrophoresis can be performed locally or by central laboratory if the country does not have local capabilities or HPLC is to be performed locally.

[redacted]

8.4.2 Electrocardiogram (ECG)

Figure 8-2 Timing of study procedures

Standard 12-lead ECGs will be performed (in the supine position) after the patient has been resting for at least 5 min (10 min resting period preferred) prior to each time point indicated in Table 8-4. Electrocardiogram assessments will be conducted as outlined. Triplicate 12 lead ECGs are to be recorded approximately 2 minutes apart. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each patient. The suggested sequence of cardiovascular data collection during study visits is ECG [redacted] first, followed by vital signs, and blood sampling.

Table 8-4 Central electrocardiogram (ECG) collection plan

Week	Day	Time	ECG Type
Screening	-28 to -1	Anytime	Triplicate 12 Lead
Week 53 Day 1		Anytime	Triplicate 12 Lead
End of Treatment (visit EOT)		Anytime	Triplicate 12 Lead
Unscheduled		Anytime	Triplicate 12 Lead

Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), Patient Number, date, and kept in the source documents at the study site.

For any ECGs with patient safety concerns, triplicate ECGs must be performed to confirm the safety finding and copies forwarded to the central ECG laboratory for assessment. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Any identifier details must be redacted e.g., patient initials, date of birth.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), a copy of the assessment is sent to the core laboratory for expedited review if applicable, and the ECG is repeated to confirm the diagnosis. If the patient is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant

[redacted]

findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator. The mean result of the ECGs will be entered into the study database and used for AE reporting.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

The results of the centrally assessed ECGs are automatically transferred into the clinical database.

Clinically significant abnormalities present at screening should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

[redacted]

8.4.4 Pregnancy and assessments of fertility

All women will have serum human chorionic gonadotropin pregnancy testing at screening in order to confirm study eligibility. Additional pregnancy testing might be performed if requested by local requirements.

For all women, serum pregnancy testing is required at screening, at Week 53 Day 1, at visit EOT, and at the end of the follow-up visit. During the study, urine pregnancy testing will be performed locally; in the patients receiving crizanlizumab, a negative test result must be obtained prior to each dosing of crizanlizumab. The positive urine test needs to be confirmed with serum test. If positive, the patient must be immediately discontinued from crizanlizumab, and Novartis must be notified (see Section 10.1.4 for pregnancy reporting requirements).

Any discontinuation of the standard care drugs in patients with a positive serum pregnancy test will be at the discretion of the investigators in accordance with the prescribing information and local institutional practice.

Local pregnancy test and associated results will not be collected on eCRF.

8.4.5 Immunogenicity

See Section 8.5.2.

8.4.6 Resource utilization

Results of one study showed that AKI occurred in approximately 46% of patients with HbSS and HbSβ^0-thal and was responsible for 5% of hospitalizations. In many cases AKI occurs as a result of VOCs and ACS and can contribute to CKD progression (Saraf et al 2018). Resource utilization data will be collected for AKI events, VOCs both complicated and uncomplicated, and other SCD complications. Complicated VOCs are defined as ACS, hepatic sequestration, splenic sequestration, and priapism.

VOCs (see Section 8.5.5.2 for VOC definition) can be managed at home or by a healthcare visit. **Healthcare visit** is defined as any visit to ER and/or hospital, which includes pain management of VOC in situ. **Managed at home** is defined as **no visit** to any medical facility and/or healthcare professional to receive treatment for VOC. Healthcare contact for medical advice is allowed.

At each study visit, the patient will be asked how many times since the previous study visit, they have been hospitalized or visited the ER due to 1) AKI events; 2) VOCs (both complicated and uncomplicated); and 3) SCD complications other than VOCs.

For each healthcare visit assessed to be due to an AKI event, VOC, or other SCD complication, the following information must be documented in the eCRF: diagnostic evaluation for the AKI event (based on AKI stages 1, 2 and 3 from KDIGO Clinical Practice Guideline for Acute Kidney Injury 2012) (KDIGO 2012), VOC episode, or other SCD complication, patient

[redacted]

treatment, route of administration and management, course, duration of the AKI event, crisis, or other SCD complication, and outcome. For patients who are treated at medical facilities other than the study site, summary documents (e.g., ER or hospital discharge summaries) will need to be obtained.

Vaso-occlusive crises managed at home (not requiring healthcare resource utilization) will be recorded in the eCRF. Patients will be asked to contact the investigator within 24 hours of VOC onset. VOCs managed at home (not requiring healthcare resource utilization) without contacting the investigator within 24 hours of onset should be captured in the corresponding VOC event page.

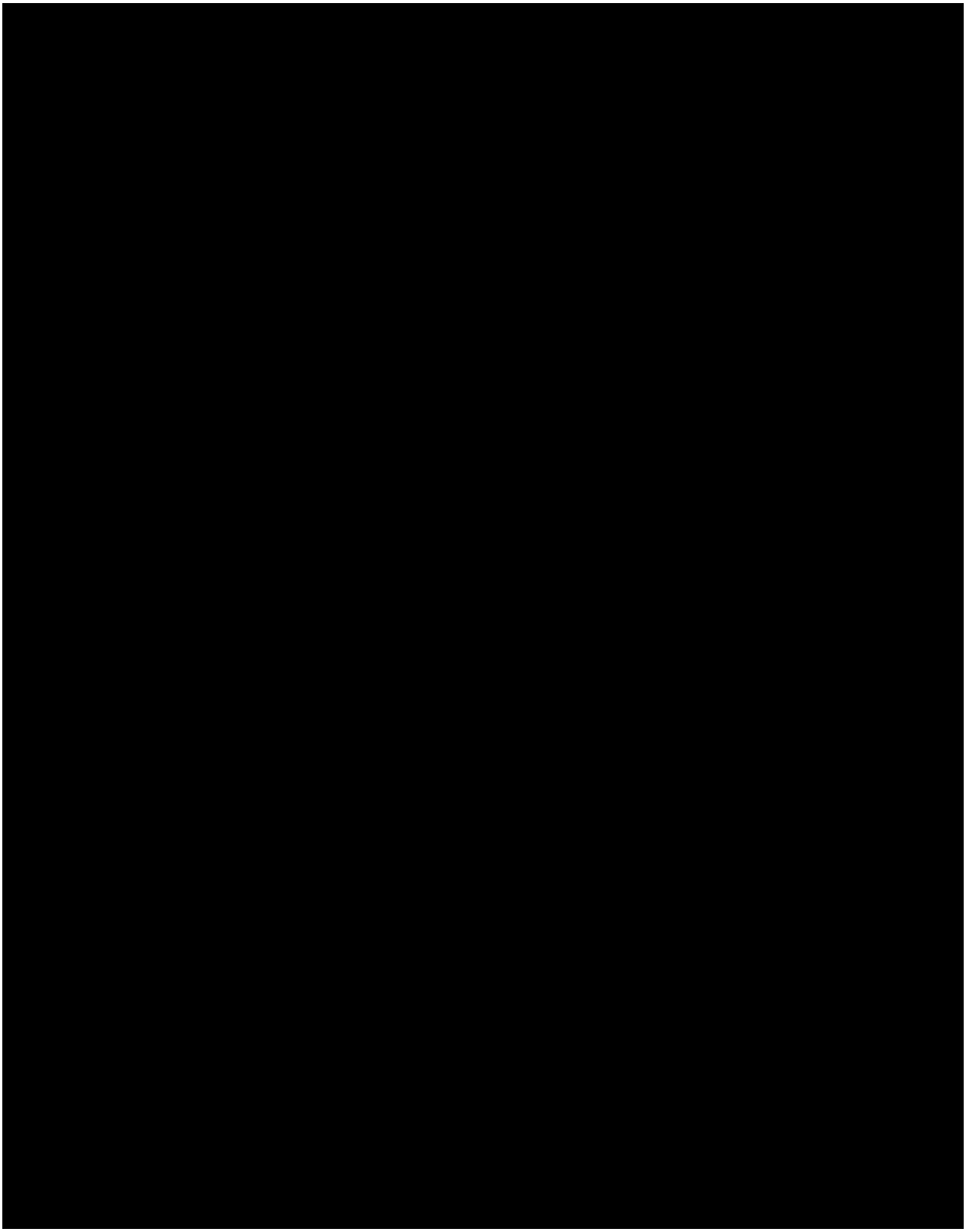
If a patient experiences an AKI event, VOC, or other SCD complication surrounding a protocol-scheduled visit day, and the patient presents for this visit, it will be counted as an AKI event that led to a healthcare visit, a VOC that led to a healthcare visit (provided the event meets the criteria for VOC discussed above), or a SCD complication that led to a healthcare visit.

8.4.7 Chest X-ray

A standard chest X-ray (PA view) will be performed at screening except for those who have had a valid X-ray done within 3 months of first dosing. Chest X-rays may be repeated during the study at the discretion of the investigator, if clinically indicated (see Section 8.5.5.2).

8.4.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.



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8.5.2 Pharmacokinetics

Crizanlizumab pre dose/trough PK samples will be collected along with immunogenicity samples at the visits defined in the assessment schedule (Table 8-1) and will be used to evaluate the impact of immunogenicity on exposure (PK). Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information. The number of samples/blood draws collected will not exceed those stated in the protocol.

Pharmacokinetic and immunogenicity assessments are not required for patients randomized to the standard of care alone arm.

8.5.2.1 Pharmacokinetic and immunogenicity blood collection and handling

At specified time points described in Table 8-6, blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For PK/immunogenicity samples, blood draws will be collected into serum separator tubes (without anticoagulant) and allowed to clot for 30 minutes (undisturbed) at room temperature. The tubes will be centrifuged for 10 minutes at approximately 3000 x g in order to separate serum. Each serum sample will be aliquoted and transferred into freezer-proof polypropylene screw-cap tubes (2 tubes for PK and 3 tubes for immunogenicity at each specified time points). The serum tubes will be frozen within 90 minutes of the blood sample collection and kept at -80ºC in an upright position until shipment and analysis.

Each serum sample should be labeled with the appropriate study, center, and patient numbers, as well as the sequential PK/immunogenicity samples and PK/immunogenicity collection number with a unique sample number. The actual collection date and time of each sample will be entered on the PK/immunogenicity blood collection eCRF pages. The exact date and time of dosing, as well as the date and actual time of blood sampling must be recorded on the appropriate eCRF. Sampling problems will be noted in the relevant field of eCRF.

Refer to the [CSEG101A2203 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK/immunogenicity samples.

[redacted]

Table 8-6 Pharmacokinetics and immunogenicity blood collection log

Week	Day	PK collection number/Dose reference ID		PK sample No	IG sample No
1	1	1	101	1	101
3	1	2	201	2	102
11	1	3	301	3	103
23	1	4	401	4	104
39	1	5	501	5	105
53	1	6	601	6	106
End of Treatment (visit EOT)	-	7	-	7	107
105-day Follow-up (as applicable)	-	8	-	8	108
Unscheduled sample[a]	-	-	-	1001+	2001+

Note: The PK samples must be taken within 24 hours before crizanlizumab administration.

[a] Including at onset and resolution of VOC event, fever, or suspected infection and at the time of transfusion (prior to and ≥ 24 hours after each of the listed events), if feasible.

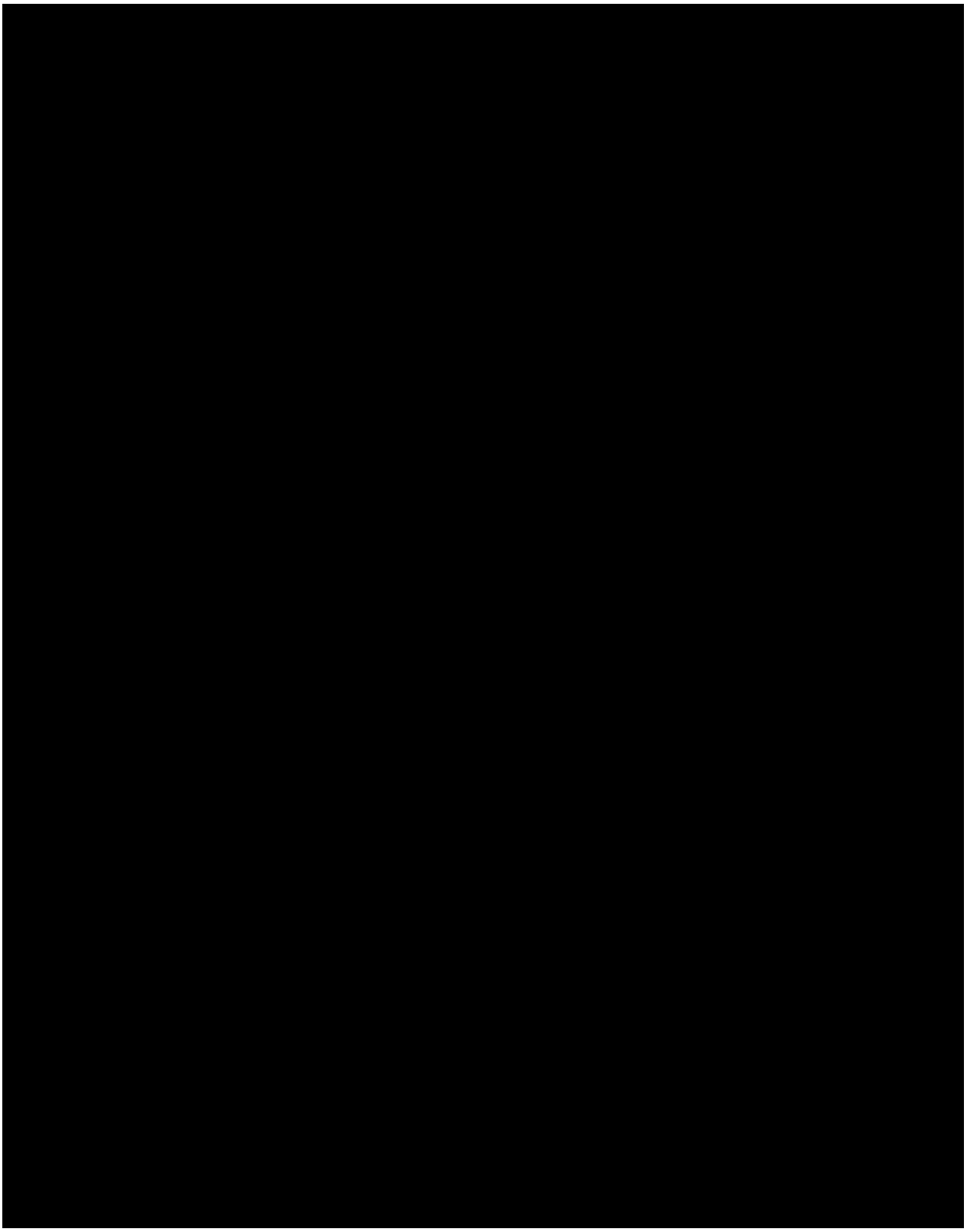
8.5.2.2 Analytical method

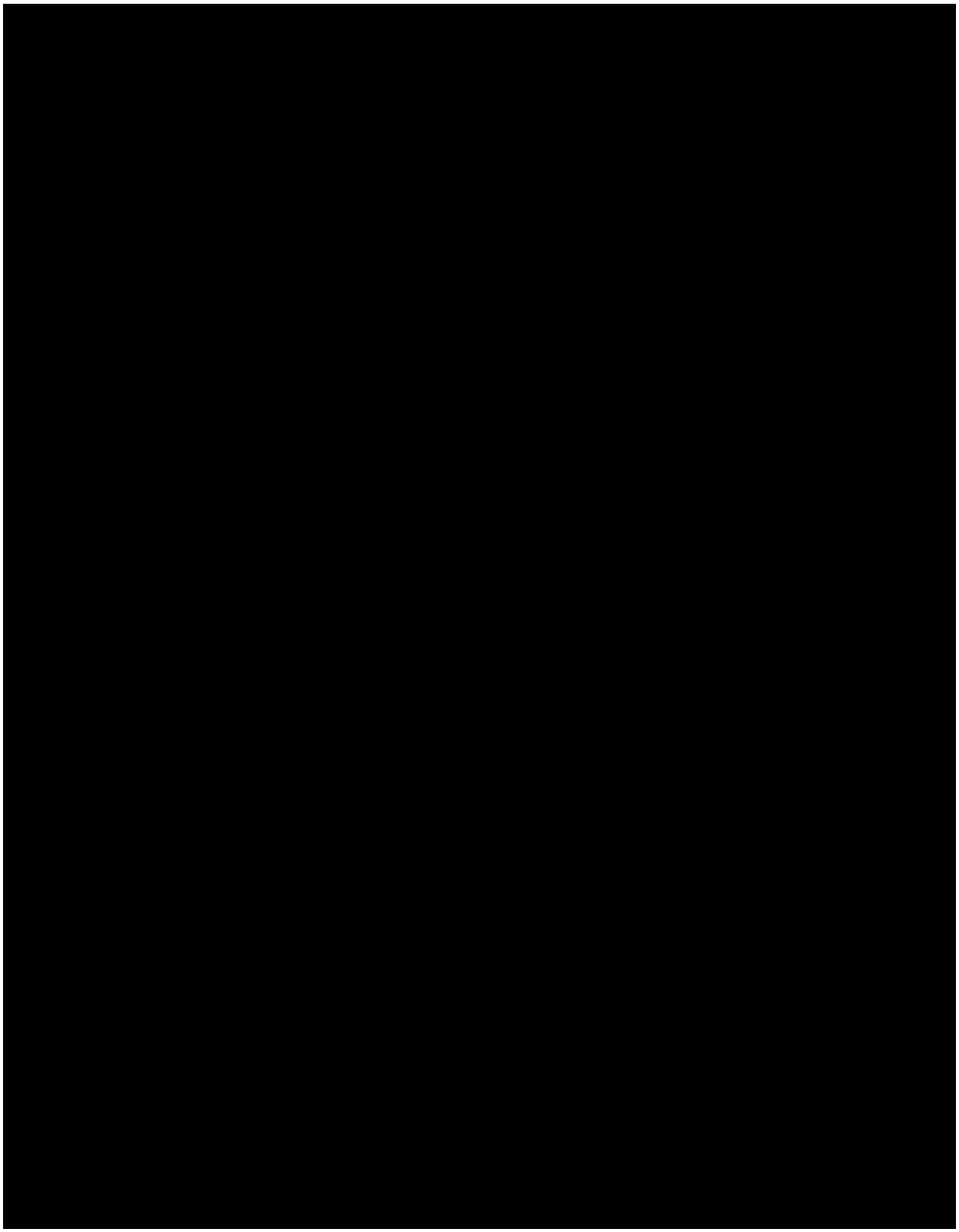
The crizanlizumab PK assay is a target capture ELISA to determine the concentration of crizanlizumab remaining in serum samples. Concentrations below the lower limit of quantification (LLOQ) will be reported as 0.00 ng/mL and missing samples will be labeled accordingly.

Immunogenicity determination will be performed using a bridging immunoassay format validated for immunogenicity screening in human serum samples.

Details of each analytical method will be given in bioanalytical data reports.

[redacted]





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8.5.5 Acute kidney injury and vaso-occlusive crisis assessments

Refer to Section 8.4.6 for resource utilization data to be collected for visits to ER and hospital due to AKI, VOCs, and/or other SCD complications.

8.5.5.1 Acute kidney injury events

Acute kidney injury will be defined based on the KDIGO Clinical Practice Guideline for AKI (KDIGO 2012):

- Increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours; or

[redacted]

- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days

Acute kidney injury will be staged based on the above KDIGO guideline and Saraf et al (2018).

8.5.5.2 Sickle cell – vaso-occlusive crisis event and other acute pain crisis

Vaso-occlusive crisis (VOC)

Vaso-occlusive crisis is defined as pain crisis (defined as an acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion) which requires therapy with oral or parenteral opioids or parenteral NSAID as well as other complicated crisis such as ACS, priapism and hepatic or splenic sequestration.

Vaso-occlusive crisis can be managed at home or by a healthcare visit. All sickle cell VOC events will be reported in the eCRF as follows:

- VOCs at home (not requiring healthcare resource utilization)
- VOCs requiring healthcare resource utilization – see Section 8.4.6

Patients should be encouraged to contact the investigator (or surrogate from the site) when they believe they are experiencing a VOC that they believe they can manage at home, both for treatment guidance and so that accurate information may be obtained for the VOC eCRF page (see Section 8.4.6).

Other acute pain crisis (APC)

In addition to VOCs as defined above, other APCs are of interest in this study. Other APC is defined as an acute episode of pain with no known cause for pain other than vaso-occlusion, and requiring treatment with analgesics other than opioids or parenteral NSAIDs.

- **Other APC leading to healthcare visit** is defined as an APC with any visit to a medical facility such as an emergency room, hospital and/or office visit, which includes pain management of that APC in situ.
- **Other APC managed at home** is defined as another APC with **no visit** to any medical facility and/or healthcare professional to receive treatment for APC

  Resolution of other APCs will match the definition of resolution of uncomplicated VOCs (see above). A participant experiencing other APCs managed at home should contact the investigator within 24h, as indicated for VOCs managed at home (see above).

During COVID-19 pandemic, if a patient experiences a VOC/other APC and other subtypes of VOC event such as hepatic/splenic sequestration, priapism and especially acute chest syndrome, testing for COVID-19 is recommended as per local guidance/practice.

Chest X-ray

[redacted]

Chest X-ray must be conducted within 3 months prior to Week 1 Day 1. Chest X-ray must be repeated during the study in case of suspected ACS and reported as an unscheduled assessment in eCRF.

Transfusions

Patients participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) are not eligible. Transfusions for acute complications are permitted (ACS, acute splenic sequestration, acute hepatic sequestration, worsened anemia) and investigators are encouraged to obtain PK/PD samples before and after the simple or exchange transfusion is administered.

Table 8-8 Vaso-Occlusive Crisis or other acute pain crisis Assessment Collection Plan

Procedure/Assessment collection plan	Screening/Baseline	During Treatment/Follow-up
Chest X-Ray[1]	Mandated (screening)	If clinically indicated
VOC or other acute pain crisis information	Mandated (screening and baseline)	Mandated, when VOC or other acute pain crisis occurs
Concomitant medication – Analgesics administration	If clinically indicated	Mandated, when VOC or other acute pain crisis occurs
Healthcare resource utilization	If clinically indicated	Mandated, when VOC occurs
Transfusion administration	If clinically indicated	If clinically indicated
Soluble biomarkers (e.g., P-selectin)	Mandated (baseline)	If possible, at time of VOC (Mandated at time points indicated in Table 8-1)
PK and Immunogenicity samples	Mandated (baseline)	Optional at onset and resolution of VOC, fever or suspected infection. Optional before and after transfusion. (Mandated at time points indicated in Table 8-1 only for patients in the crizanlizumab + standard of care arm)

[1] Within 3 months of Week 1 Day 1

8.5.5.3 Missed school or work

At each study visit, the patient will be asked how many full days of school or work they have missed due to AKI, VOCs, and/or other SCD complications since their previous visit. This information will be recorded in the eCRF.

8.5.6 Trial Feedback Questionnaire (optional)

This trial will include an option for subjects to complete an anonymized questionnaire, 'Trial Feedback Questionnaire'. The intention of this questionnaire is to collect subject feedback on

[redacted]

their clinical trial experience. Individual subject level responses will NOT be reviewed by investigators. Novartis will use these responses to understand where improvements can be made in the clinical trial process. This questionnaire DOES NOT collect data about the subject's disease, symptoms, treatment effect or adverse events, and therefore would not be trial data. Should any spontaneous information be collected about AEs, this would be transferred to the clinical and safety databases.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation

Discontinuation of study treatment for a patient occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration) and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment (crizanlizumab and/or at least one standard of care medication) for a given patient if, he/she believes that continuation would negatively impact the patient's well-being.

Crizanlizumab must be discontinued under the following circumstances:

- Patient/guardian decision
- Pregnancy
- Lactation
- Grade 3 and 4 IRRs and other specified grade 4 ADRs and dose interruptions of crizanlizumab due to toxicity (see Section 6.5.1.1)
- Use of prohibited treatment (see Section 6.2.2), except as noted in Section 6.2.2
- Any other protocol deviation that results in a significant risk to the patient's safety
- Other reasons for earlier termination may include but are not limited to:
    - Decision based on recommendations from applicable board(s) after review of safety data
    - Discontinuation of study drug development
- One or more standard of care drugs must be discontinued under the following circumstances:
- Patient/guardian decision
- If deemed medically necessary by the patient's physician (see Section 6.5.1.2)
- If a patient requires renal replacement therapy (i.e. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation)

If discontinuation of study treatment occurs (crizanlizumab and/or at least one standard of care drug), the investigator should make a reasonable effort to understand the primary reason for the

[redacted]

patient's premature discontinuation of the study treatment and record this information. Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). Patients who discontinue treatment early will return for a Week 53 urine ACR/PCR assessment. The Week 53 urine ACR/PCR assessment should occur 12 months after the first dose of study treatment.

If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, and letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the patient's study treatment discontinuation.

9.1.2 Discontinuation from study

Discontinuation from study is when the patient permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason. If the patient agrees, a final evaluation at the time of the patient's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Withdrawal of informed consent/Opposition to use data/biological samples

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use data/biological samples occurs when a patient:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use patient's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent/opposition to use data/biological samples and record this information.

[redacted]

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the patient therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Crizanlizumab must be discontinued (i.e., patients in the crizanlizumab + standard of care arm) and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

If the patient agrees, a final evaluation at the time of the patient's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), for regulatory or medical reasons, or if crizanlizumab development is discontinued.

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, the study site must contact the patients who must be seen as soon as possible (within 7 days, if possible, or by their next scheduled visit) for an EOT visit and treated as a patient who discontinued from study treatment. If the patient is in the crizanlizumab + standard of care arm, crizanlizumab will be discontinued (unless the decision to provide post-trial access to crizanlizumab has been made and is appropriate, see Section 9.2). Patients will then be followed in the mandatory safety follow-up period for two safety assessments 30 days (phone call) and 105 days (study visit, as applicable) after the visit prior to the EOT visit (i.e., 30 days and 105 days after the last crizanlizumab dose for patients randomized to crizanlizumab + standard of care). If the EOT visit occurs ≥ 30 days after the previous visit the 30-day phone call is not required. Patients who will receive crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105

[redacted]

day follow-up. The end of the safety follow-up period for these patients will be the 30-day follow-up. All other patients are required to complete the 105-day follow-up.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last patient completes their safety follow-up or Week 53 urine ACR/PCR assessment (if patient discontinues study treatment early) and any repeat assessments associated with this visit have been documented and followed up appropriately by the investigator or, in the event of an early study termination decision, the date of that decision.

For individual patients, the study will be completed when the patient finishes their safety follow-up or Week 53 urine ACR/PCR assessment (if patient discontinues study treatment early) and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator. Patients who will receive crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up. The end of the safety follow-up period for these patients will be the 30-day follow-up. All other patients are required to complete the 105-day follow-up.

The final analysis will occur at the end of the study. All available data from all patients up to this cut-off date will be analyzed and summarized in a final CSR.

Patients who participate in Novartis clinical trials and are deriving benefit from the treatment based on the investigator's evaluation may receive post-trial access to the treatment.

In addition, per investigator discretion and assessment of potential risk/benefit, the investigator may apply for access to crizanlizumab for patients randomized to the standard of care alone arm. Patient eligibility will be reviewed upon submission to Novartis.

In the context of this study, Post-Trial Access (PTA) means the provision of investigational treatment to clinical trial participants following trial completion.

Post-Trial Access will continue until the investigational treatment receives regulatory approval, is commercially available and a reimbursement decision has been made in the patient's country, or the patient is no longer deriving benefit per the investigator's evaluation. Safety will continue to be monitored while the patient receives PTA to the investigational drug.

Mechanisms for the provision of investigational treatment may include a post study drug supply (PSDS), a rollover protocol, provision of the drug in the respective indication outside of a clinical trial setting if no further safety or efficacy data is needed, or other mechanisms appropriate for the country.

The PTA mechanism must comply with the local laws and regulations in the participating trial countries. If Novartis discontinues the development of the study treatment due to reasons which

may include when study results are negative, Novartis will work with the investigators to transition the patients onto suitable locally available treatment or alternative treatment.

10 Safety monitoring and reporting

During a public health emergency (i.e. COVID-19 pandemic) that limits or prevents on-site study visits, regular phone calls will occur for safety monitoring and discussion of the patient´s health status until the patient can again visit the site. This telephone contact should preferably be done according to the study visit schedule, or more frequently if needed.

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events eCRF under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. AEs will be assessed and graded according to the CTCAE version 5.0.
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication – SCD-related CKD) the assessment of causality will usually be ‘Not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.

[redacted]

5. action taken regarding with study treatment.
   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased (only applicable for standard of care medications)
   - Drug interrupted/withdrawn
6. its outcome (i.e., recovery status or whether it was fatal)
   If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For Grade 3 and 4 AEs only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until the completion of the safety follow-up period (i.e., 30-day safety follow-up or the 105day follow-up visit [as applicable]).

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Adverse events of special interest include events that are known class effects, were identified pre-clinically or in prior clinical studies, or may be clinically relevant based on the mechanisms of action of crizanlizumab and the disease under study. Adverse events of special interest include the following, but may not be limited to:

- Infections
- IRRs
- Effect on hemostasis (hemorrhage)
- Immunogenicity

Adverse events of special interest will be defined in the most recent version of the electronic case retrieval sheet for crizanlizumab trials available at the time of a database lock for an analysis.

Progression of CKD (CTCAE Grade 1 [eGFR lower limit of normal to 60 mL/min/1.73 m^2] and CTCAE Grade 2 [eGFR 59 to 30 mL/min/1.73 m^2] only), if documented by use of appropriate method (e.g., per the KDIGO guidelines for definition and identification of CKD progression KDIGO 2013), should not be reported as an AE/SAE (see Section 10.3).

Information about ADRs for the investigational drug can be found in the IB.

[redacted]

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of [or worsening of any pre-existing]) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening
  Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an ER or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in

[redacted]

hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered an SAE irrespective if a clinical event has occurred (Section 10.1.5).

10.1.3 SAE reporting

To ensure patient safety, every SAE must be reported, regardless of causality, occurring after the patient has provided informed consent and until completion of the safety follow-up period (ie. 30-day safety follow-up or 105-day follow-up period (as applicable). If the patient discontinues from the study early, SAEs must be reported to Novartis safety immediately, without undue delay, and under no circumstances later than within 24 hours of learning of its occurrence until the end of the safety follow-up period. Patients who will receive crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105 day follow-up. The end of the safety follow-up period for these patients will be the 30-day follow-up. All other patients are required to complete the 105-day follow-up.

Serious AEs occurring after provision of informed consent until the time the patient is deemed a screen failure must be reported to Novartis.

Information about all SAEs is collected and recorded on the electronic Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to the study treatment, complete the eSAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow-up information is submitted in the same way as the original SAE Report and should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

[redacted]

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 105-day period after the Week 51 Day 1 visit or if the patient discontinued the study early, 105-days after the last dose of discontinued study treatment, should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The patient must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. Pregnancy in patients who received crizanlizumab should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO & PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported

[redacted]

to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional safety monitoring

10.2.1 Liver safety monitoring

Refer to Section 6.5.2.1 Follow up on potential drug induced liver injury cases.

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Data Monitoring Committee

This study will include a DMC which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial safety data and recommend to the sponsor whether to continue, modify, or terminate a trial. The timing of the safety DMC analyses will be defined in the DMC Charter, as described in Section 12.7.

The DMC will consist of clinicians specialized in SCD and/or CKD. Details of the role of the DMC will be described in the DMC charter.

10.2.3 Steering Committee

The Steering Committee (SC) will be established comprising SCD experts, nephrology experts and investigators participating in the trial (i.e., not being members of the DMC) and Novartis/sponsor representatives from the CTT.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the CTT, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in the SC charter.

[redacted]

10.3 Protocol exempt adverse events and serious adverse events

Progression of CKD (CTCAE Grades 1 and 2 only), if documented by use of appropriate method (e.g., per the KDIGO guidelines for definition and identification of CKD progression KDIGO 2013), will be a Protocol Exempt AE and SAE for the current study. Information to confirm disease progression (i.e., eGFR) will be recorded in the eCRF. CKD progression (CTCAE Grades 1 and 2 only) SHOULD NOT be reported as AEs or SAEs for the purpose of this study. CKD progression (CTCAE Grades 1 and 2 only) will not be considered as an SAE in regards to reporting requirements. Additional events or complications which are not CKD progression itself will be reported as AE/SAEs. Details will be given in the eCRF completion guidance.

Protocol Exempt AEs and SAEs implemented in the SEG101 program include VOCs and other acute pain crisis, which must be reported on the VOC/other acute pain crisis page in the eCRF. As VOCs and other APCs will be analyzed for evaluation of efficacy, AEs and SAEs involving VOCs or other acute pain crisis SHOULD NOT be reported as AEs or SAEs for the purpose of this study. These events will not be considered as SAEs in regards to reporting requirements. All details, procedures and hospitalizations which are directly related to the VOC, e.g., ventilation of a patient with ACS are considered part of the VOC and will not be reported as AE/SAEs but entered on the applicable eCRF page. Additional events or complications which are not VOCs itself will be reported as AE/SAEs. Details will be given in the eCRF-completion guidance.

In case that new information arises which changes the diagnosis of a VOC, i.e., gives another medically determined explanation than vaso-occlusion in the opinion of the investigator, the event has to be reported according to the rules of Section 10.1 and must be reported to Novartis within 24 hours of learning of the new information.

However, in case a VOC event is suspected to be related to study treatment, and/or results in a fatal outcome, it will be reported as SAE in addition to recording on the VOC eCRF page.

The events in Section 8.5.5.2 are the VOCs and other acute pain crisis that will not be reported as AEs/SAEs (see also Section 10.3).

11 Data collection and database management

11.1 Data collection

All data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source.

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web enabled software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements, investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for [data discrepancies in the eCRFs, allow modification

[redacted]

and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on eCRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated contract research organization (CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

Randomization codes and data about crizanlizumab dispensed and used by the patient and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

Deoxyribonucleic acid samples: To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the patient's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the patient's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database. [redacted]

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eSource DDE or

[redacted]

eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture/data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original ICF signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12 Data analysis and statistical methods

The primary efficacy and safety analyses will be conducted on all patient data at the time the trial ends (see Section 9.2 for the definition of study completion).

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

A patient is considered to be enrolled into the study if signed informed consent has been obtained. Only patients with signed informed consent will be included in the analysis data sets.

12.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

12.1.2 Safety Set

[redacted]

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

12.2 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics will be summarized descriptively by treatment groups. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum will be presented.

The analyses will be based on the FAS.

12.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration in weeks of crizanlizumab, as well as the dose intensity (computed as the ratio of total dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity), will be listed and summarized for all patients. The duration in weeks will also be summarized for the standard of care medications for both arms.

The number of patients with dose adjustments (interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed for crizanlizumab. The number of patients with dose adjustments (interruption, reduction, increase, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed for standard of care medications.

Concomitant medications and significant non-drug therapies/procedures prior to and after the start of the study treatment, as well as the incidence of transfusion, will be summarized for all patients by treatment arm.

The Safety Set will be used.

12.4 Analysis supporting primary objectives

12.4.1 Definition of primary endpoint

The primary endpoint of the study is the proportion of patients with ≥ 30% decrease in ACR at 12 months from baseline.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint will be descriptively analyzed based on the data from the FAS. A logistic regression model that includes effects for treatment and randomization stratification factors will be utilized. The treatment effect based on the log odds ratio will be estimated by the model

[redacted]

The odds ratio for the relative difference between treatments in the primary endpoint, and its corresponding 95% confidence interval, will be presented.

In addition, the proportions of patients in each group with at least a 30% decrease in ACR will be presented, along with a 95% 2-sided confidence interval for the difference in proportions.

Details of the statistical model and methods will be described in the SAP.

12.4.3 Handling of intercurrent events of primary estimand

The primary estimand is described by the following attributes:

1. The target population comprises patients with kidney dysfunction due to SCD.
2. The primary variable is proportion of patients with ≥ 30% decrease in ACR at 12 months.
3. The treatment of interest is the effect of crizanlizumab 5.0mg/kg + standard of care on the ACR value taken for the entire study duration with or without the intercurrent events
4. The intercurrent events are the events occurring after randomization that may impact the treatment effect. The intercurrent events of interest are:
   a) Treatment discontinuation
   b) Initiation or discontinuation of HU/HC, HA approved form(s) of L-glutamine, ACE and/or ARB
   c) Intake of NSAIDs within 48 hours prior to ACR measurement
   d) Intake of voxelotor
   e) Blood transfusion or VOC occurred within 7 days of urine and blood sample collection
   f) Renal replacement therapy (i.e. hemodialysis, peritoneal dialysis, hemofiltration and kidney transplantation)
5. The summary measure is the odds ratio of the treatment effect for patients with ≥ 30% decrease in ACR between crizanlizumab + standard of care and standard of care alone.

Handling of the intercurrent events

The approach of accounting for intercurrent events is as follows:

- **For the intercurrent events 3.a:** The composite strategy will be applied for treatment discontinuation due to death of any cause, drug-related AEs, and progressive disease. Define treatment discontinuation due to death of any cause, drug-related AEs, and progressive disease as non-responders. The hypothetical strategy will be applied for treatment discontinuation due to other reasons. The interest focuses on the treatment effect if patients stay on treatment for 12 months, if possible.
- **For the intercurrent events 3.b:** The hypothetical strategy. The interest focuses on the treatment effect if patients had not initiated or discontinued HU/HC, HA approved form(s) of L-glutamine, ACE and/or ARB.
- **For the intercurrent events 3.c:** The hypothetical strategy. The interest focuses on the treatment effect if patients had not received NSAIDs within 48 hours prior to ACR measurement.

[redacted]

- **For the intercurrent events 3.d:** The hypothetical strategy. The interest focuses on the treatment effect if patients had not received voxelotor.
- **For the intercurrent events 3.e:** The hypothetical strategy. The interest focuses on the treatment effect if patients had not had blood transfusion or VOC occurred.
- **For the intercurrent events 3.f:** The composite strategy will be applied for treatment discontinuation due to renal replacement therapy, define treatment discontinuation due to renal replacement therapy as non-responders. The hypothetical strategy will be applied if the renal replacement therapy occurred and patient did not discontinue. The interest focuses on the treatment effect if patients had not had renal replacement therapy.

The primary estimand is described in Table 12-1 below, together with its key attributes. The estimand outlined below will be described in further detail in the SAP.

[redacted]

Table 12-1 Primary estimand

Estimand	Target population	Summary Measure	Handling of the intercurrent events	Rationale
Primary estimand	Patients with kidney dysfunction due to SCD	Odds ratio of treatment effect on ACR response	Exclude ACR data collected after treatment discontinuation. Treatment discontinuation due to death of any cause, drug-related AEs, progressive disease will be considered as non-responders; other reasons will use multiple imputation (MI). Exclude ACR data after initiation or discontinuation of HU/HC, HA approved form(s) of L-glutamine, ACE and/or ARB. Will use MI. Exclude ACR data collected after intake of NSAIDs within 48 hours prior to ACR measurement. Will use MI. Exclude ACR data collected after intake of Voxelotor. Will use MI. Exclude ACR data collected after blood transfusion or VOC occurred (if within 7 days before the ACR measure). Will use MI. Exclude ACR data collected after renal replacement therapy. Treatment	See Section 12.4.3 Handling of the intercurrent events

[redacted]

Estimand	Target population	Summary Measure	Handling of the intercurrent events	Rationale
			discontinuation due to renal replacement therapy will be considered as non-responders; If the patient required renal replacement therapy and did not discontinue study treatment, will use MI.	

[redacted]

12.4.4 Sensitivity analyses

No sensitivity analyses will be conducted.

12.4.5 Supplementary analyses

No supplementary analyses will be conducted.

12.5 Analysis supporting secondary objectives

The secondary objectives in this study are to describe the two treatment groups with respect to albuminuria/proteinuria, including change in ACR, ACR decline rate, PCR improvement and stable, and with respect to eGFR, percentage change in eGFR, eGFR decline rate, and the progression of CKD as defined in Section 8.3.4, safety, and healthcare resource utilization. Another secondary objective is to assess the immunogenicity and accompanying PK of crizanlizumab.

The secondary efficacy endpoints will be summarized descriptively using the FAS. For all safety endpoints, the Safety Set will be used.

12.5.1 Efficacy endpoints

The mean change in ACR from baseline to 3, 6, 9, and 12 months of treatment

The mean change in ACR from baseline will be summarized and plotted over time by treatment arm. An Analysis of Covariance (ANCOVA) model that includes effects for treatment, randomization stratification factors, and baseline ACR, will be carried out for analysis.

The slope of ACR decline from baseline to 12 months of treatment based on ACR values at baseline and at 3, 6, 9, and 12 months

The slope of ACR decline will be estimated as a random coefficient in a linear mixed effect model: the model will be fitted to ACR data collected at baseline and at Months 3, 6, 9, and 12. It includes treatment, stratification factors, time and the interaction of treatment by time as the fixed effects, and intercept as a random effect. The mean slopes within each treatment and the difference in mean slopes between two treatments will be presented. The percentage change in eGFR from baseline to 3, 6, 9, and 12 months of treatment

The percentage change in eGFR is calculated as the post-baseline eGFR value minus the baseline eGFR divided by the eGFR at baseline. The calculation of eGFR is based on the CKD-EPI (for patients ≥ 18 at screening) and Creatinine-based “Bedside Schwartz” (for patients < 18 at screening) equations. Percentage change in eGFR from baseline will be summarized and plotted over time by treatment arm. An ANCOVA model that includes effects for treatment, HU/HC use (Yes vs. No), and baseline eGFR, will be carried out for analysis using a logarithmic scale.

[redacted]

The slope of eGFR decline from baseline to 12 months of treatment based on eGFR values at baseline and at 3, 6, 9, and 12 months

The slope of eGFR decline will be estimated as a random coefficient in a linear mixed effect model: the model will be fitted to eGFR data collected at baseline and at Months 3, 6, 9, and 12. It includes treatment, stratification factors, time and the interaction of treatment by time as the fixed effects, and intercept as a random effect. The mean slopes within each treatment and the difference in mean slopes between two treatments will be presented.

Other secondary efficacy endpoints

The following proportion related efficacy endpoints will be analyzed by the same statistical methods described in the primary endpoint analysis section. In addition, a shift table will be provided for patients with progression of CKD for each treatment.

The proportion of patients with ≥ 30% decrease in ACR at 6 months from baseline

The proportion of patients with PCR improvement and stable PCR (improvement: ≥ 20% decrease in PCR from baseline; stable: within ± 20% change from baseline) at 12 months from baseline

The proportion of patients with progression of CKD from baseline to 12 months

Details of the statistical methods will be described in the SAP.

12.5.2 Safety endpoints

Safety assessments will consist of monitoring and recording all AEs, based on CTCAE v5.0. It will also include regular monitoring of laboratory assessments including hematology and clinical chemistry, cytokines, complement, tryptase, p-selectin, urinalysis, measurement of vital signs, and physical examination. ECG assessments will be done at screening, Week 53 Day 1, visit EOT, and as clinically indicated.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to Day -1 (i.e., the day before first dose of crizanlizumab/day before the Week 1 Day 1 visit)
2. On-treatment period: from Day 1 (i.e., day of first dose of crizanlizumab/day of Week 1 Day 1 visit) to 105 days after last dose of discontinued study treatment or the end of the safety follow-up period (i.e., 30 or 105 days after the Week 51 Day 1 visit)
3. Post-treatment period: starting at Day 106 after last dose of discontinued study treatment or Day 31 or 106 after the Week 51 Day 1 visit.

Adverse events

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of AE, relation to study treatment.

[redacted]

Serious AEs, non-serious AEs, and AESIs during the on-treatment period will be summarized.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and SAEs (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

All vital signs data will be summarized by treatment and visit/time.

12-lead ECG

12-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each patient during the study. ECG data will be read and interpreted centrally.

All ECG data will be summarized by treatment and visit/time.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per National Cancer Institute CTCAE Version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

Common Terminology Criteria for AEs Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5.0

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline
- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

Immunogenicity

Immunogenicity will be measured pre-dose on Week 1 Day 1, during treatment, at visit EOT, and at the 105-day follow-up visit (as applicable).

All immunogenicity results will be listed and summarized for the crizanlizumab + standard of care treatment group by patient and visit/time.

Immunogenicity will be characterized descriptively tabulating ADA incidence on-treatment.

[redacted]

Resource utilization

Annualized rate of visits to ER and hospitalizations due to AKI events, VOCs, or other SCD complications will be used to evaluate the healthcare resource utilization (visits to clinic, ER and hospitalizations) in crizanlizumab + standard of care arm and standard of care alone.

12.5.3 Pharmacokinetics

Crizanlizumab pre-dose/trough PK samples will be taken to accompany immunogenicity measurements to evaluate the impact of immunogenicity on exposure (PK) (see Section 12.5.2).

Crizanlizumab predose serum concentration data will be summarized for the crizanlizumab + standard of care treatment arm by patient and visit/sampling time point. Descriptive summary statistics will be provided for the crizanlizumab + standard of care treatment arm by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Descriptive summary statistics will include mean (arithmetic and geometric), SD, coefficient of variance (CV; arithmetic and geometric), median, minimum and maximum.

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

Formal interim analyses are not planned. However, safety DMC analyses will be performed at specified time points, as defined in the DMC Charter. Additional DMC meetings may be scheduled if unexpected safety findings arise.

12.8 Sample size calculation

The sample size was adjusted to reflect current recruitment status.
When the estimation based approach for the 95% CI for the difference between treatment arms is used to calculate the precision estimates with sample size of 25 patients per treatment arm (total N=50 patients without drop-outs), then the width is 0.429 and the precision (half of the width) is around 0.215. See Table 12-3 for the 95% CI calculation of the difference (30% - 10%) varying the sample size per arm from 10 to 40.

Table 12-3 Confidence Intervals for the Difference between Two Proportions using Proportions Numeric Results for Two Sided Confidence Intervals for the Difference in Proportions Confidence interval method: Chi – Square – Simple Asymptotic (Pearson)

Confidence Level	N1	N2	Allocation Ratio	Actual Width	P1	P2	P1-P2	Lower Limit	Upper Limit
0.95	10	10	1.000	0.679	0.300	0.100	0.200	-0.139	0.539
0.95	15	15	1.000	0.554	0.300	0.100	0.200	-0.077	0.477
0.95	20	20	1.000	0.480	0.300	0.100	0.200	-0.040	0.440
0.95	25	25	1.000	0.429	0.300	0.100	0.200	-0.015	0.415
0.95	30	30	1.000	0.392	0.300	0.100	0.200	0.004	0.396
0.95	35	35	1.000	0.363	0.300	0.100	0.200	0.019	0.381
0.95	40	40	1.000	0.339	0.300	0.100	0.200	0.030	0.370

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, Article 3 Part 2 of the Directive 2005/28/EC, and US CFR Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming

[redacted]

his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as *clinicaltrials.gov* and as required in EudraCT. In addition, after study completion (see study completion definition in Section 9.2) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written SOPs as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

[redacted]

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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16 Appendices

Not applicable.

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