Official Title: An Indian Multi-centric Phase IV Study to Assess the Safety of Crizanlizumab With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Vaso-occlusive Crises.

NCT Number: NCT04662931

Document Date: Clinical Study Protocol: 27-July-2020

Appendix 16.1.1 Protocol and protocol amendments

History of changes	
Version	**Summary of changes**
1.0	Original version

1 Protocols and protocol amendments

Table 1-1 List of protocols, protocol amendments and post text supplements

Document	Effective Date
Original Protocol	27-Jul-2020

NOVARTIS

Novartis Research and Development

SEG101 (crizanlizumab)

Clinical Trial Protocol CSEG101A2403

An Indian Multi-centric Phase IV study to assess the safety of Crizanlizumab with or without hydroxyurea therapy in sickle cell disease patients with vaso-occlusive crises.

Document type:	Clinical Trial Protocol
EUDRACT number:	2020-003625-31
Version number:	00 (Original Protocol)
Clinical Trial Phase:	IV
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Table of contents

List of tables

List of figures

List of abbreviations

ACS	Acute Chest Syndrome
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APC	Acute Pain Crisis
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
BUN	Blood Urea Nitrogen
CDS	Core Data Sheet
CFR	Code of Federal Regulation
CI	Confidence Interval
CK	Creatinine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CO	Country Organization
COVID-19	Coronavirus disease of 2019
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCGI	Drug Controller General of India
DDE	Direct Data Entry
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines agency
EOS	End of Study
EOT	End of Treatment
eSource	Electronic Source

FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	Hour
Hb	Hemoglobin
HbC	Hemoglobin C
HBcAb	Hepatitis B core Antibody
HbS	Hemoglobin S
HbS/β^0 or HbS/β^+	Hemoglobin S with β^0-thalassemia or β^+-thalassemia
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HbSS	Homozygous hemoglobin S
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HDL	High Density Lipoproteins
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HSV	Herpes simplex virus
HU/HC	hydroxyurea/hydroxycarbamide
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
IG	Immunogenicity
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LDL	low density lipoproteins
LFT	Liver function test
LLN	lower limit of normal
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
OTC	Over the counter
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PSGL-1	P-selectin glycoprotein ligand-1
PT	prothrombin time
PTT	Partial thromboplastin time
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RBC	red blood cell(s)
SAE	Serious Adverse Event
SCD	Sickle Cell Disease
SCT	Sickle cell trait
SD	standard deviation
SEG101	Novartis humanized anti-P-selectin monoclonal antibody variant
SelG1	Reprixys humanized anti-P-selectin monoclonal antibody variant
SOP	standard operating procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
ULN	upper limit of normal
US	United States
USD	United States dollar
USPI	US Package Insert
VOC	Vaso-occlusive crisis
WHO	World Health Organization
WoC	Withdrawal of Consent

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 background therapy)
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 participant
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which screening was completed successfully and participant is ready to receive first dose
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Investigational drug/ treatment	The drug whose properties are being tested in the study. Investigational treatment does not include other treatments (i.e HU/HC and L-glutamine) administered as concomitant background therapy allowed by the protocol when used within approved indication/dosage.
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)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
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	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study

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 or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant or as defined as per protocol
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Protocol summary

Protocol number	CSEG101A2403
Full Title	An Indian multi-centric Phase IV study to assess the safety of Crizanlizumab with or without hydroxyurea therapy in sickle cell disease patients with vaso-occlusive crises
Brief title	Study of safety of crizanlizumab in Indian patients with sickle cell disease
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the safety of crizanlizumab in Indian patients with sickle cell disease aged 16 years or older with history of vaso-occlusive crisis to in accordance with permission no. IMP/BIO/20/000026 to import and market crizanlizumab by the Drug Controller General of India (DCGI) and the requirement to conduct a local Phase IV safety study
Primary Objective(s)	The primary objective of this study is to assess the serious adverse events of crizanlizumab in Indian patients with sickle cell disease
Secondary Objectives	The secondary objective of this study is to assess the overall safety and tolerability of crizanlizumab in Indian patients with sickle cell disease
Study design	This is a Phase IV non-randomized, open label, single-arm, interventional, multicenter study to evaluate the safety of crizanlizumab at a dose of 5.0 mg/kg in addition to standard of care for 12 months, in patients with sickle cell disease and a history of vaso-occlusive crisis leading to healthcare visit
Study population	This study will enroll 140 participants with confirmed diagnosis of sickle cell disease who have had a history of vaso-occlusive crisis leading to a healthcare visit The participants will be 16 years or older, who may or may not be receiving hydroxyurea/hydroxycarbamide for treatment
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study • Male or female participants aged 16 years and older on the day of signing informed consent • Confirmed diagnosis of sickle cell disease by hemoglobin electrophoresis or high performance liquid chromatography • Concomitant sickle cell therapy with hydroxyurea/hydroxycarbamide is permitted • History of vaso-occlusive crisis leading to healthcare visit prior to screening visit as determined by medical history and investigator assessment • Participants must meet the following central laboratory values at the screening visit:

	• Absolute Neutrophil Count ≥1.0 x 10^9/L • Platelet count ≥75 x 10^9/L • Hemoglobin: for adults (Hb) ≥4.0 g/dL and for adolescents (Hb) ≥5.5 g/dL • Glomerular filtration rate ≥ 45 mL/min/1.73 m^2 using CKD-EPI formula • Direct (conjugated) bilirubin < 2.0 x ULN • Alanine Aminotransferase (ALT) < 3.0 x ULN • ECOG Performance Status ≤2 for adults and Karnofsky Performance Scale ≥ 50% for adolescents
Key Exclusion criteria	• Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation. History of severe hypersensitivity reaction to other monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction • participant has received crizanlizumab and/or other P-selectin inhibitor prior to the study or plans to receive it during the duration of the study. • 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 • Participant has documented immunogenicity to a prior biological drug • Participants who are on active treatment with Voxelotor, other investigational drug or other monoclonal antibody, or intend to initiate the same during the course of the trial • Pregnant females or females who have given birth within the past 90 days or who are breastfeeding, and women of child-bearing potential unless they are using effective methods of contraception during dosing and for 15 weeks after stopping treatment • Clinically significant bleeding disorder • Positive test for hepatitis C ribonucleic acid (HCV RNA). • Malignant disease • participant has significant active infection (i.e. HIV, hepatitis B , COVID-19 infections) or immune deficiency (including chronic use of immunosuppressive drugs)
Study treatment	Crizanlizumab (SEG101) at 5.0 mg/kg dose
Treatment of interest	Not applicable
Efficacy assessments	Not applicable
Key safety assessments	• Monitoring of adverse events and serious adverse events • Vital signs • Hematology, chemistry, coagulation and urinalysis • Electrocardiograms at relevant time points • Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab

Additional assessments	• Pharmacokinetic parameters • Vaso-occlusive events
Data analysis	This is a descriptive study and no hypothesis testing will be conducted However the primary endpoint which is the proportion of patients reporting a serious adverse event over the treatment period, will be presented with a 2-sided 95% confidence interval
Key words	Sickle cell disease, crizanlizumab, safety, vaso-occlusive crisis

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Sickle cell disease (SCD) is a genetic blood disorder, caused by a single missense mutation (Glu6Val) in the β-globin gene, which early on progresses into a systemic disease. Vaso-occlusion is the hallmark of SCD and can lead to serious acute and chronic complications. Vascular dysfunction, inflammation, and P-selectin mediated cell-to-cell and cell-to-endothelium adhesion play an important role in the pathophysiology of SCD. Vaso-occlusive crisis (VOC) is the most common clinical manifestation of SCD. Every VOC increases morbidity and can result in organ damage/failure and/or death (Ballas et al 2010, Brousseau et al 2010, Powars et al 2005). Additionally, VOCs lead to significant health care utilization and are the most common cause of emergency room visits and hospital admissions in SCD patients, with total medical costs exceeding 1.1 billion USD annually (Kauf et al 2009).

SCD 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 conditions are also common among people of Mediterranean countries, Africa, Middle East, India, Caribbean and parts of South and Central America. In India, existing prevalence data suggest that there may be 18 million subjects with sickle cell trait (SCT) and 1.4 million SCD patients among the tribal population (Saxena et al 2017).

The most frequent and typically most severe form is homozygous HbSS (sickle cell anemia) (α_2 βs2, HbS). Other forms of SCD include compound heterozygous conditions, such as hemoglobin C (HbC) with HbS (HbSC), HbS with β-thalassemia (HbS/β^0-thalassemia or HbS/β^+-thalassemia), and HbS with other variants (Ware et al 2017). Clinical signs appear within the first 6 months of life, but there is considerable variability in severity (Gill et al 1995) resulting from genetic and environmental factors. Patients describe acute pain crises (APCs) and chronic pain clearly as the most debilitating effects on their lives, affecting them physically and emotionally. Fatigue and cognitive effects also emerge as other debilitating effects. In addition, organ-damage and long-term complications have also a severe effect on them. As a result of these complications, patients often have reduced quality of life (QoL), significant anxiety, depression, and short-life expectancy (Kanter and Kruse-Jarres 2013).

Current treatment:

Stem cell bone transplantation remains the only curative modality for SCD patients. However, a limited number of patients are eligible, and substantial concerns remain about transplant-related mortality and long-term toxicities, including infertility (Ware et al 2017).

Blood transfusions are commonly used as a single transfusion to ameliorate acute, even life-threatening complications, and/or as chronic transfusions to prevent long-term complications most frequently related to stroke prevention.

Vaso-occlusive crises are typically treated symptomatically with pain management and with other supportive care (Bender, MA 1993, Rees et al 2010). Severe pain is often treated with opioids but their use is controversial due to the risk of opioid-related adverse events.

Preventive treatments to reduce the number of VOCs are limited. Hydroxyurea/hydroxycarbamide (HU/HC) is approved to reduce the frequency of painful crises and the need for transfusions in SCD patients aged 2 and older with a history of recurrent, moderate-to-severe painful crises. HU/HC presents several limitations, including significant toxicities, need for blood monitoring, leading to poor patient compliance. HU/HC is cytotoxic, myelosuppressive and teratogenic, potentially carcinogenic, impacts fertility (Charache et al 1995, Pászty et al 1997, Sicklos-USPI 2017, Droxia-USPI 2012), and has a number of contraindications/special warnings and precautions for use.

Crizanlizumab has been approved by the US FDA on 15-Nov-2019, to reduce the frequency of VOCs in adult and pediatric patients aged 16 years and older with SCD. As of 14-July-2020, approval has been granted in 8 countries including India.

Other therapies, approved by the US FDA but not in India:

- L-glutamine (Endari™) was approved by the FDA in July-2017 to reduce acute complications associated with SCD in patients aged ≥5 years old. The mechanism of action of the amino acid L-glutamine in treating SCD is not fully understood. L-glutamine decreases oxidative state in red blood cells (RBCs). Oxidative stress phenomena are involved in the pathophysiology of SCD. Sickled RBCs are more susceptible to oxidative damage than normal RBCs, which may contribute to the chronic hemolysis and vaso-occlusive events associated with SCD.
- Voxelotor is a novel hemoglobin S (HbS) polymerization inhibitor for the treatment of SCD approved by the FDA in November-2019. Voxelotor regulates the affinity of Hb for oxygen, resulting in a decrease in the concentration of deoxygenated sickle hemoglobin which forms polymers.

Despite the use of HU/HC, transfusions, and/or L glutamine patients with SCD may still experience VOC. Therefore, SCD is a life-threatening disease with severe morbidities and represents a major unmet medical need.

1.1.1.1 Role of P-selectin in VOC

The recognition that adherence of leukocytes, platelets and sickled RBC to blood vessel endothelium and to each other have a primary role in VOC led to further research into the selectins, which mediate the first steps in the recruitment of leukocytes to specific tissues. P-selectin is the best characterized of the selectins and binding specificity and affinity to its physiological ligand P-selectin glycoprotein ligand-1 (PSGL-1) is well-documented (McEver 2004, Mehta et al 1998).

Extensive data suggests a pivotal role for P-selectin in the pathophysiology of SCD (Matsui et al 2001). Using mice engineered or altered to express human hemoglobin S (sickle cell hemoglobin) investigators have demonstrated P-selectin mediates cell-cell and cell-endothelium interactions between the endothelium and sickled RBC, leukocytes, and platelets. All of these interactions have been implicated in SCD vaso-occlusion. Further, blockade or

genetic absence of P-selectin decreases or eliminates these interactions and vaso-occlusion. Taken together, these studies establish P-selectin as a key mediator of vaso-occlusion in SCD.

1.1.2 Introduction to investigational treatment

1.1.2.1 Overview of 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 PSGL-1. Extensive pre-clinical data have established P-selectin as a key mediator of VOC in SCD (Matsui et al 2001) and suggest that its blockade could eliminate or reduce VOC.

The compound was previously developed by Reprixys Pharmaceuticals Corporation under the investigational drug code SelG1. Novartis acquired the company on 18-Nov-2016, and is now the drug developer and sponsor for crizanlizumab, under the investigational drug code, SEG101. First global approval for crizanlizumab for SCD treatment has been obtained from the US FDA on 15-Nov-2019.

[Crizanlizumab Investigator's Brochure] provides detailed information related to toxicology, nonclinical pharmacology, drug properties and preclinical data.

1.1.2.2 Clinical experience

As of the safety cut-off date of the last [Crizanlizumab Investigator's Brochure] (31-Mar-2020), 523 subjects, including 95 healthy volunteers, have been enrolled into crizanlizumab clinical program, including two Reprixys–sponsored studies with Reprixys–manufactured crizanlizumab SelG1, and six Novartis-sponsored studies (one completed and five ongoing) with Novartis manufactured crizanlizumab SEG101.

Crizanlizumab was received by 23 patients, as a part of Managed access program ([CSEG101A2001M]) and by 1 patient, as a part of a post-study drug supply product program following completion of previous Phase II ([CSEG101A2201] – SUSTAIN).

In SUSTAIN study, the 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.

The substantial efficacy and acceptable safety of crizanlizumab demonstrate an overall favorable benefit-risk profile and warrant further clinical development in SCD.

1.2 Purpose

The purpose of this study is to evaluate the safety of crizanlizumab in Indian SCD patients aged 16 years or older with history of VOC in accordance with permission no. IMP/BIO/20/000026 to import and market crizanlizumab by the Drug Controller General of India (DCGI) and the requirement to conduct a local Phase IV safety study.

1.2.1 Study rationale and purpose

Globally, SCD is a neglected chronic disorder of increasing health importance with estimates suggesting India to have the second highest burden of disease (Hockham et al 2018).

Based on the data from the SUSTAIN study ([CSEG101A2201]), marketing authorization for crizanlizumab in India and other countries has been obtained.

However, the SUSTAIN study did not include Indian patients and the ongoing crizanlizumab global clinical trials include relatively small numbers of Indian patients.

This phase IV multi-center study will be conducted in India to evaluate the safety of crizanlizumab at a dose of 5 mg/kg in patients with SCD and history of VOC leading to healthcare visit.

2 Objectives and endpoints

Objectives and related endpoints are described in Table 2-1 below.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the serious adverse events (SAEs) of crizanlizumab in Indian patients with SCD	• Frequency, severity and causality of SAEs during the treatment period
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the overall safety and tolerability of crizanlizumab in Indian patients with SCD	• Frequency, severity and causality of treatment emergent adverse events (including Adverse Events of Special Interest (AESI)), as well as labs, vital signs, ECGs and immunogenicity

3 Study design

This is a Phase IV open label, single-arm, interventional, multicenter study to evaluate safety of crizanlizumab at a dose of 5.0 mg/kg in addition to standard of care in Indian patients with SCD and a history of VOC leading to healthcare visit.

The study will include 140 participants aged 16 years and older with confirmed diagnosis of SCD (all genotypes are eligible) who have had a history of VOC leading to a healthcare visit prior to screening visit. Participants may receive HU/HC, L-glutamine (Endari™) or erythropoietin-stimulating agents as treatment/concomitant medication for SCD before and during the study.

The enrollment period for this study is expected to be approximately 24 months.

Screening

Within 35 days before enrollment, written informed consent, according to local guidelines, will be signed by the participants, and prior to any study related screening procedures are performed. All screening evaluations must be performed during the screening period.

Treatment

An Interactive Response Technology (IRT) system will be used to confirm eligibility, enroll the participant and dispense the uniquely numbered treatment packages.

Participants will receive crizanlizumab 5.0 mg/kg via intravenous (i.v.) infusion on Week 1 Day 1, followed by a second dose 14 days later (Week 3 Day 1), and then every 4 weeks. Participants will receive crizanlizumab for approximately 12 months (until week 51) in the trial or until unacceptable toxicity, death, are lost to follow-up or discontinued from crizanlizumab for any other reasons at the discretion of the investigator or the participant.

Following study treatment discontinuation, participants will perform an end of treatment visit.

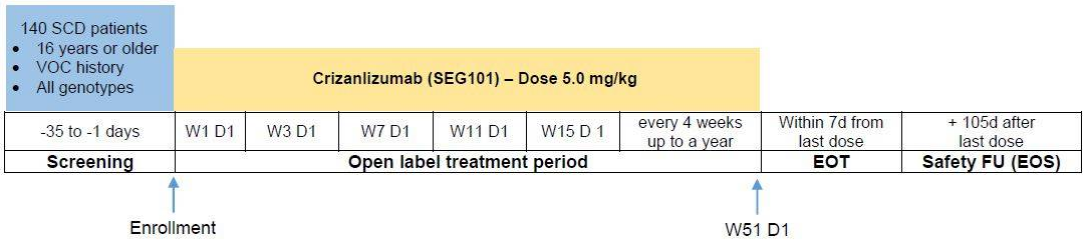
Post-treatment follow-up

After the end of treatment visit, all participants will be followed up for safety up to 105 days (15 weeks) after the last infusion of investigational study drug. In case the participant switches to non-study crizanlizumab within this period, all the assessments are still performed as per the Table 8-1 and crizanlizumab obtained from other sources as study drug supply will be recorded as concomitant medication.

For participants who in the opinion of the investigator are still deriving clinical benefit from crizanlizumab, every effort will be made to continue provision of crizanlizumab via a roll over trial or other available options at the time.

The end of the study (EOS) will occur when all the patients have either completed or discontinued the study treatment and/or the 105 days follow-up period. The final analysis will occur at the EOS. All available data from all patients up to the trial end and will be analyzed and summarized in a final CSR.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

This is a multicenter phase IV study that will be conducted in India to assess the safety of crizanlizumab with or without HU/HC in SCD patients with vaso-occlusive crises.

This is a descriptive study and no hypothesis testing will be conducted, but rather is designed to assess safety of crizanlizumab at the 5 mg/kg dose in Indian SCD patients (Section 12.8.1).

4.2 Rationale for dose/regimen and duration of treatment

Participants will receive crizanlizumab at the approved dose of 5.0 mg/kg by i.v. infusion over 30 minutes. Dose number 2 is administered as a loading dose 2 weeks following the first dose to rapidly achieve steady-state serum concentrations. This is followed by repeated administration of the same dose every 4-weeks ± 7 days (until week 51, see Section 6.1.5) to ensure that steady-state serum concentrations of crizanlizumab are maintained to provide a consistent blockade of P-selectin throughout the study.

The treatment period will be approximately 12 months, in line with the pivotal study SUSTAIN.

The eligibility criteria and the design of this study will enable assessment of the safety of crizanlizumab in patients representative of current SCD clinical practice and management in India.

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

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

There is no planned interim analysis before the conduct of the primary analysis.

4.5 Risks and benefits

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.

Pooled safety data from the SUSTAIN and [CSEG101A2202] studies in patients treated with crizanlizumab 5 mg/kg (n=111 patients, Oct-2019 cut-off) showed that crizanlizumab is generally associated with a favorable safety profile. Adverse drug reactions (ADRs) were nausea (16.2%), back pain (15.3%), arthralgia (14.4%), pyrexia (14.4%), abdominal pain (9.0%), diarrhea (8.1%), pruritus (7.2%), vomiting (5.4%), myalgia (4.5%), musculoskeletal chest pain (4.5%), oropharyngeal pain (3.6%), infusion site reaction (2.7%), and infusion-related reaction (1.8%).

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, the mechanism of action of crizanlizumab, identified and potential risks include the following:

Infusion-related reactions (IRRs)

Administration of mAbs can be associated with IRRs. A focused search for potentially "severe" IRRs (i.e. indicative of hypersensitivity/anaphylaxis or cytokine-release syndrome) identified 2 (1.8%) patients treated with crizanlizumab 5 mg/kg in the pooled data set; the reported term was infusion-related reaction, none of which was serious. Severe IRRs including cases requiring hospitalization have been described in ongoing clinical trials and the post-marketing setting.

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 28.8% of patients 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 (8.1%), arthralgia and back pain (4.5%), and fatigue and myalgia (2.7%). None of these events were grade 3 or grade 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%). 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.

Immunogenicity

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

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 pharmacokinetic/pharmacodynamic (PK/PD) or safety profile with ADA development. Immunogenicity (IG) and development of ADA will be monitored during the study.

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 43.2% patients in the safety pool. The most frequently reported infections were urinary tract infection (9.9%), upper respiratory tract infections (8.1%), pneumonia and sinusitis (4 patients each, 3.6%). Most infections were low in severity (grade 1 or 2). In the randomized SUSTAIN study, the frequency of 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 increased 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.

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, abnormal laboratory parameters of the hemostatic system, or thrombosis. In the safety pool, a search for hemorrhagic events identified 13 (11.7%) patients, mostly related to abnormal laboratory findings. Except for prolonged prothrombin time (PT) reported in 3 (2.7%) patients, 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, consistent with hemolysis and the underlying disease.

In Study [CSEG101A2201], 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, participants 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 not further identify any patients with AEs related to thrombosis in the 5 mg/kg pooled data, suggesting that crizanlizumab does not have a relevant pro-aggregant or pro-thrombotic effect.

Laboratory test interference with automated platelet counts

Laboratory interference with automated platelet counts (platelet clumping) has been observed in patients treated with crizanlizumab in clinical studies, in particular when tubes containing EDTA (ethylenediaminetetraacetic acid) 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.

To mitigate the potential for this laboratory test interference, it is recommended to run respective test as soon as possible (within 4 hours of blood collection) or use citrate tubes. When needed, platelet counts can be estimated via a peripheral blood smear. Additional details are provided in Section 8.4.1 of protocol and the [CSEG101A2403 laboratory manual].

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 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 i.v. 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.

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 6.2 . 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.

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

5 Study Population

CSEG101A2403 will enroll 140 participants with confirmed diagnosis of SCD of any genotype who have had a history of VOC leading to a healthcare visit. No replacement will be done for participants that discontinue early. The study will include participants aged 16 years or older, who may or may not be receiving HU/HC for SCD.

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

5.1 Inclusion criteria

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female participants aged 16 years and older on the day of signing informed consent.
3. Confirmed diagnosis of SCD by hemoglobin electrophoresis or high performance liquid chromatography (HPLC) [performed locally]. All SCD genotypes are eligible, genotyping is not required for study entry.
4. Concomitant sickle cell therapy with HU/HC is permitted.
5. History of VOC leading to healthcare visit prior to screening visit as determined by medical history and investigator assessment.
6. Participants must meet the following central laboratory values at the screening visit:
   - Absolute Neutrophil Count $\geq 1.0 \times 10^9$/L
   - Platelet count $\geq 75 \times 10^9$/L
   - Hemoglobin: for adults (Hb) ≥4.0 g/dL and for adolescents (Hb) ≥5.5 g/dL
   - Glomerular filtration rate ≥ 45 mL/min/1.73 m^2 using CKD-EPI formula
   - Direct (conjugated) bilirubin < 2.0 x ULN

- Alanine Aminotransferase (ALT) < 3.0 x ULN

7. ECOG performance status ≤2 for adults and Karnofsky Performance Scale ≥ 50% for adolescents.

5.2 Exclusion criteria

1. Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation. History of severe hypersensitivity reaction to other monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction.
2. Participant has received crizanlizumab and/or other P-selectin inhibitor prior to the study or plans to receive it during the duration of the study.
3. 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.
4. Any condition which, in the opinion of the investigator, is likely to interfere with the successful collection of the measurements required for the study.
5. Participant has documented immunogenicity to a prior biological drug.
6. Participants who are on active treatment with Voxelotor, other investigational drug or other monoclonal antibody, or intend to initiate the same during the course of the trial.
7. Pregnant females or females who have given birth within the past 90 days prior screening or who are breastfeeding.
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using highly effective methods of contraception during dosing and for 15 weeks after stopping treatment.

   Highly effective contraception methods include:

   - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. 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 tubal ligation at least six weeks before taking study treatment. 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 participants on study the vasectomized male partner should be the sole partner for that participant
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), 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 taking study treatment. 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)

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. 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 child bearing potential.

9. Clinically significant bleeding disorder.
10. Participant with active HIV infection (detectable viral load).
11. Participant with active Hepatitis B infection (HBsAg positive) will be excluded. Note: Participant with antecedent but not active Hepatitis B (i.e. anti-HBc positive, HBsAg and HBV-DNA negative) are eligible.
12. Positive test for hepatitis C ribonucleic acid (HCV RNA). Note: Participant 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 IFN-free regimes) or ≥ 12 months (with the use of IFN-based regimes) after cessation of antiviral treatment are eligible.
13. 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.
14. Participant has significant active infection or immune deficiency (including chronic use of immunosuppressive drugs).

6 Treatment

6.1 Study treatment

The sponsor will supply the investigational product crizanlizumab (SEG101) as an open label medication. Investigational treatment will be administered by i.v. infusion on Week 1 Day 1, followed by a second dose 14 days later (Week 3 Day 1), and then administration will take place every 4 weeks until week 51.

6.1.1 Investigational and control drugs

Crizanlizumab (SEG101) is supplied in individual single use glass vials each containing 10.0 mL of concentrate for solution for infusion. The crizanlizumab formulation is supplied at a concentration of 10 mg/mL.

On infusion day, the pharmacist or designated personnel will prepare an individual dose of crizanlizumab to study participants (as assigned by the IRT system) diluted in 0.9% saline sodium chloride solution or 5% dextrose infusion bags. Refer to the [CSEG101A2403 Pharmacy Manual] for further instructions on dose regimen and dose preparation.

Study drug will be administered over 30 minutes by i.v. infusion.

Table 6-1 Investigational and control drug

Investigational Drug	Pharmaceutical Dosage Form and Route of Administration	Dose	Frequency and/or regimen
Crizanlizumab (SEG101) 10mg/ml	Concentrate for solution for i.v. infusion	5.0 mg/kg	Week 1 Day 1, Week 3 Day 1, and Day 1 of every 4-weeks cycle until Week 51 Day 1

There is no control drug in this single-arm open label trial.

6.1.2 Additional study treatments

No other study treatment beyond crizanlizumab is included in this trial.

6.1.3 Treatment arms/group

This is a single-arm study where all participants will receive crizanlizumab (SEG101) at the dose of 5.0 mg/kg.

6.1.4 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to Section 6.5.1 and Section 6.5.2.

Participants who permanently discontinued the study for any reason should follow the protocol safety assessments as scheduled. After discontinuing study treatment, further treatment is left to the physician's discretion.

6.1.5 Treatment duration

The total duration of treatment in the study for each participant is planned to be approximately 12 months (a total of 51 weeks).

Participants may be permanently discontinued due to unacceptable toxicity, death, lost to follow-up or discontinued from the study treatment for any other reasons at the discretion of the investigator or the participant.

Every effort will be made to supply crizanlizumab after the end of the trial to participants who may benefit from continued treatment as per the Investigator's opinion.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant joined the study must be recorded on the appropriate Case Report Forms (CRF).

In general, the use of any concomitant medication/therapies deemed necessary for the care of the participant is permitted, except as specifically prohibited (see Section 6.2.2).

The participant must be told to notify the investigational site about any new medications he/she takes within 30 days prior to initial dosing until the completion of end of study (EOS) visit (through 105 days after the last dose of study treatment). 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 EOS visit must be listed on the Prior and Concomitant Medications and Surgical and Medical Procedures page of the CRF.

Concomitant sickle cell therapy with HU/HC is permitted. However, for participants who are receiving, or for whom the investigator is considering to initiate, treatment with HU/HC, it is recommended that HU/HC treatment has been initiated at least 3 months prior to study entry.

Erythropoietin-stimulating agents are also permitted to manage chronic symptomatic anemia. L-glutamine oral powder (Endari™) is also permitted without restriction. Please refer to Section 6.2.1.1 for over-the counter forms of L-glutamine.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and prophylactic doses of anticoagulants are permitted as per local guidance, while other anti-platelets 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 per standard of care. Other approved medications for supportive care (antiemetics, anxiolytics, hypnotics, antihistamines) are permitted, including marinol (dronabinol, tetrahydrocannabinol).

There is no restriction on administration of inactivated vaccines during this trial.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Although Endari™, the FDA-approved version of L-glutamine, is permitted, other over-the-counter 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, jujbe, angelica sinensis, lovage) 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.

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

Avoid any live vaccines against infectious diseases within 4 weeks prior to the first dose of investigational treatment. There is no restriction on the administration of inactivated vaccines during the study.

Infusion-related reactions have been reported in patients treated with crizanlizumab. Prophylactic pre-medication is permitted, and sites should follow local practice or guidelines for administration of monoclonal antibodies; pre-medications may be adjusted based on clinical presentation as deemed appropriate (e.g. for pain management). Steroids should be used with caution in SCD patients (Brandow et al 2020).

If a participant experiences a grade 3 or grade 4 infusion related reaction, study drug must be discontinued (see Table 6-2).

In the event that a major surgery becomes necessary, it is recommended to hold crizanlizumab for at least 4 weeks prior to the procedure, and then restarted once the patient has fully recovered, at the investigator discretion.

6.2.2 Prohibited medication

The use of voxelotor is prohibited during the study.

The use of other investigational drugs is prohibited during the study. In addition, the administration of monoclonal antibodies other than the investigational treatment is prohibited, due to the theoretical potential for cross-reactivity and/or overlapping toxicities with other monoclonal antibodies. If voxelotor, other investigational agents or other monoclonal antibodies 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 the Screening visit.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a participant Number (participant No.), that is assigned when the participant is registered for screening and is retained for the participant throughout his/her participation in the trial. A new participant No. will be assigned if the participant is re-screened.

The participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing a new informed consent form, the participant is assigned to the next sequential participant No. available.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study.

All participants who fulfill all inclusion/exclusion criteria will be assigned to be treated with crizanlizumab. The IRT system will assign the study medication kits to be dispensed at each participant visit.

6.4 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the Clinical Trial Team (CTT).

6.5 Dose escalation and dose modification

Investigational drug dose escalation is not permitted.

For dose interruption please refer to Section 6.5.1.

6.5.1 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions are either recommended or mandated (see Table 6-2). Dose reductions are not allowed.

If drug-induced toxicities are present, participants are required to be closely monitored. Subsequently, a decision to continue or discontinue the participant from the study would have to be determined.

These dose interruption guidelines are summarized in the table below. Deviations from mandatory dose interruptions are not allowed. Furthermore, permanent treatment discontinuation is mandatory for specific events as indicated in the table below.

These dose interruptions must be recorded in the Study Treatment CRF.

Every effort should be made to maintain the participant 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 point, every effort should be made to bring the participant's infusions back onto the protocol-defined schedule (within the ±7 day window).

In the event that a major surgery becomes necessary, it is recommended to hold crizanlizumab for at least 4 weeks prior to the procedure, and then restarted once the patient has fully recovered, at the investigator discretion.

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 study treatment 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 participants, re-testing is encouraged if signs or symptoms indicative of COVID-19 newly develop or persist. Participants with suspected infection who tested negative, may continue study treatment.

In case of trial participants who have been exposed to someone infected by COVID-19 and in self-quarantine, administration of the study treatment should be delayed until the trial participant completes the quarantine and remains asymptomatic and/or COVID-19 has been ruled out.

Table 6-2 Criteria for dose interruption and re-initiation of crizanlizumab treatment for adverse drug reactions.

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (CTCAE version 5) during a cycle of therapy	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3) and Grade 2 (ANC < 1500 - 1000/mm^3)	Recommendation: continue study treatment.
Grade 3 (ANC < 1000 - 500/mm^3)	Mandatory: interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists, permanently discontinue study treatment.
Grade 4 (ANC < 500/mm^3)	Mandatory: permanently discontinue study treatment.
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.3°C)	Mandatory: interrupt dose until resolved or next dose schedule. If abnormality persists, permanently discontinue study treatment.
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3) and Grade 2 (PLT < 75,000 - 50,000/mm^3)	Recommendation: continue study treatment.
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Recommendation: interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists, permanently discontinue study treatment.
Grade 4 (PLT < 25,000/mm^3)	Mandatory: interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists, permanently discontinue study treatment.
Investigations (Hepatic)	
Isolated Direct Bilirubin	
Grade 1 >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	Recommendation: continue study treatment.
Grade 2 and 3 (>1.5 - 10.0 x ULN if baseline was normal; >1.5 - 10.0 x baseline if baseline was abnormal)	Recommendation: interrupt study treatment. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline. Monitor for hemolysis. If resolved to ≤ Grade 1 or baseline, then continue study treatment.
Grade 4 (>10.0 x ULN if baseline was normal;	Mandatory: permanently discontinue study treatment.

>10.0 x baseline if baseline was abnormal)	
Isolated ALT elevation	
Grade 1 (> ULN - 3.0 x ULN if baseline was normal; 1.5 -3.0 x baseline if baseline was abnormal)	Recommendation: continue study treatment.
Grade 2 (> 3.0 - 5.0 x ULN if baseline was normal; > 3.0 - 5.0 x baseline if baseline was abnormal)	Recommendation: continue study 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 or baseline. If resolved, then continue with next dose scheduled. If abnormalities persist >2 weeks, refer to Section 6.5.2.1 for additional follow-up evaluations as applicable.
Grade 3 (> 5.0 - 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal)	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, to ≤ 3.0 x ULN or baseline, then continue study treatment.
Grade 4 (> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal)	Mandatory: permanently discontinue study treatment.
Combined elevations of ALT and bilirubin (direct (conjugated))	
• For participants with normal baseline ALT and direct bilirubin value: ALT >3.0 x ULN combined with direct bilirubin >2.0 x ULN OR • For participants with elevated baseline ALT or direct bilirubin value: ALT>2x baseline AND > 2.0 x baseline direct bilirubin	Mandatory: interrupt study treatment. Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results, follow-up for symptoms and initiate workup for competing etiologies. Then with weekly monitoring of LFTs[b], or more frequently if clinically indicated, until ALT and direct bilirubin have resolved to ≤ Grade 1 or baseline or stabilization over 4 weeks. Study drug may be restarted only if another etiology has been identified and liver enzymes have returned to ≤Grade 1 or baseline. If DILI (drug-induced liver injury) is confirmed, permanently discontinue study treatment. Refer to Section 6.5.2.1 for additional follow-up evaluations as applicable.

Infections	
Grades 1 and 2	Recommendation: continue study treatment
Grade 3	Mandatory: interrupt dose until resolved. If resolved, then continue with next dose scheduled.
Grade 4	Mandatory: permanently discontinue study treatment.
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 paticipant 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, opioids, i.v. fluids); prophylactic medications indicated for <=24 hrs	Recommendation: • 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 (e.g. analgesics such as paracetamol/acetaminophen or NSAIDs and anti-histamines) 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 (50% rate or slower) under continuous observation. Ensure a minimum of 1 hour observation period prior to restarting the infusion. • Administer premedication before restarting (e.g.analgesics such as paracetamol/acetaminophen or NSAIDs and anti-histamines within 1 hour prior to dosing) if not done already to manage the event, as per local institutional guidelines for prophylaxis of infusion related reactions, including subsequent infusions. • In case of recurring infusion reactions despite premedication and prolonged infusion, consider discontinuation of study treatment.
Grade 3 and 4	Mandatory: • Permanently discontinue study treatment and initiate appropriate medical care.

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	

General Note: Decision for dosing is made on prior lab results. 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] Common Terminology Criteria for Adverse Events (CTCAE Version 5)
[b] Core Liver Function Tests (LFTs) consist of ALT, AST, GGT, LDH, total bilirubin (fractionated [direct and indirect]) ALP, albumin and creatinine kinase (CK).

6.5.2 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, 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 such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All participants must be followed up for adverse events and serious adverse events for 105 days following the last doses of crizanlizumab.

6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Participants with an elevation of transaminases in combination with an increase of total bilirubin (TBIL) and a normal ALP may be indicative of potentially severe DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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 BIL will be required in this criteria.

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

- **For participants with normal ALT and Direct BIL value at baseline:** ALT > 3.0 x ULN combined with Direct BIL > 2.0 x ULN
- **For participants with elevated ALT or Direct BIL value at baseline:** ALT > 2.0 x baseline AND Direct BIL > 2.0 x baseline
- **For participants with normal ALT at baseline:** ALT > 5.0 x ULN for more than 2 weeks
- **For participants with elevated ALT at baseline:** ALT >3.0 x baseline for more than 2 weeks

For these participants, repeat LFTs as soon as possible, preferably within 48-72 hours. Participants should be closely monitored and workup for competing etiologies initiated including hemolysis or cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2.

Note: (The R value is calculated by dividing the ALT by the ALP (alkaline phosphatase), 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 ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of an alternative explanation, these participants should be immediately discontinued from study treatment. 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 alkaline phosphatase.

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 local testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

4. Additional local testing for other hepatotropic viral infection (CMV, EBV or HSV), 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

Compliance will be assessed by administration of the study treatment under the supervision of the investigator or his/her designee. This information must be captured in the source document and in the Drug Accountability Form.

6.7 Preparation and dispensation

Each study site will be supplied with investigational treatment in packaging as described in the Pharmacy Manual. A unique medication number is printed on the study medication label. Crizanlizumab solution will be prepared by a pharmacist or designated personnel appropriately qualified and trained in the preparation procedure in accordance with the [CSEG101A2403 Pharmacy Manual].

Participants should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, flushing, pruritus, rash, hypotension, hypoxemia, and fever, and vital signs monitored more frequently if clinical indicated, in accordance with the Pharmacy Manual. The same applies for the subsequent infusions, if medically indicated. If a participant experiences an IRR (see Table 6-2), he/she may receive pre-medication on subsequent dosing days as per institutional standard of care, at the discretion of the treating physician. Please refer to Section 6.2.1.1 regarding use of corticosteroids.

If a participant experiences a Grade 3 or 4 IRR, the participant will discontinue investigational treatment. Please refer to Table 6-2.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the [Crizanlizumab Investigator's Brochure] .

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements in India. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, 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.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

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

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent

possible given his/her understanding. If the participant 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 participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH 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 Investigator's Brochure (IB) (and/or CDS for marketed drugs). This information will be included in the participant informed consent and should be discussed with the participant 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 (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- Main study consent for parent/legal guardian to give consent for their child
- Model participant information and adolescent assent for16 and17 years old participants to express their understanding of the purpose of this study and what will happen if their parent(s)/legal guardian(s) give their consent for their participation in this study
- Pregnancy Outcomes Reporting Consent for female participants

Women of child bearing 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.

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

8 Visit schedule and assessments

Table 8-1 lists all assessments and indicates with an "X" (for data captured in the database) or "S" (for data documented in medical files) the visits at which they are performed.

All data obtained from these assessments must be supported in the participant’s source documentation.

No CRF will be used as a source document.

Allowed visit windows are specified as follows:

Screening assessments, apart from those listed below, must occur within 35 days prior to the enrollment as per Table 8-1.

There is a ± 7 day visit window permitted for every dosing visit (with a minimum of 21 days to be respected between 2 doses following Week 3 Day 1), except Week 3 Day 1 where a visit window of ±3 days is allowed (and dose is given within 14±3 days of Week 1 Day 1 dose).

Participants who discontinue the study for any reason 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 End of Treatment (EOT) will be performed.

All participants will be followed in the mandatory safety follow-up period which includes safety assessments at 105 days after the Week 51 Day 1 visit, or, if the participant discontinued the study early, at 105 days after the last dose of the discontinued study treatment. A + 7 days for the end of follow-up period (last infusion + 105 days) is allowed.

Every effort should be made to follow the schedule outlined in Table 8-1.

Table 8-1 Assessment Schedule

Period	Screening	Treatment														End of Treatment (EOT)	Follow Up Phase
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	EOT	Safety Follow Up (EOS)
Days	-35 to -1	1	15	43	71	99	127	155	183	211	239	267	295	323	351	Within 7days of last dose	105 days after last dose
Informed consent	X																
IRT Registration	X															X	X
IRT Enrollment[1]		X															
Study Disposition	X															X	X
Demography	X																
Inclusion / Exclusion criteria	X																
ECOG/Karnofsky performance status	X																
Medical History	X																
Sickle Cell – VOC History	X																
Sickle Cell – Reasons for Non-Administration of HU/HC[2]	X																
Hepatitis screen	X																
HIV screen	X																
COVID-19 testing[3]	X	if required															
Physical Examination	S																

Period	**Screening**	**Treatment**														**End of Treatment (EOT)**	**Follow Up Phase**
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**	**EOT**	**Safety Follow Up (EOS)**
Days	**-35 to -1**	**1**	**15**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**	**323**	**351**	**Within 7days of last dose**	**105 days after last dose**
Abbreviated physical examination		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Height	X															X[4]	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X			X			X			X			X	X	
Clinical Chemistry	X	X	X			X			X			X			X	X	
Coagulation	X	X	X			X			X			X			X	X	
Urinalysis	X	X	X			X			X			X			X	X	
Pregnancy Test (serum)	S															S	S
Urine Pregnancy Test		S	S	S	S	S	S	S	S	S	S	S	S	S	S		
Immunogenicity		X	X			X			X			X			X		X
Pharmacokinetics		X	X			X			X			X			X		X
Electrocardiogram (ECG)	X														X		X
Sickle cell – VOC event	X	Continuous															
Prior/concomitant medications	X	Continuous															

Period	**Screening**	**Treatment**														**End of Treatment (EOT)**	**Follow Up Phase**
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**	**EOT**	**Safety Follow Up (EOS)**
Days	**-35 to -1**	**1**	**15**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**	**323**	**351**	**Within 7days of last dose**	**105 days after last dose**
Concomitant non-drug therapies/procedures	X	Continuous															
Adverse Events[5]	X	Continuous															
Serious Adverse Events	X	Continuous															
Study drug administration		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] IRT enrollment call to be performed at Week 1 Day 1 so that the patient can start receiving medication
[2] Prior treatment with HU/HC and reason why treatment has been interrupted will be collected at Screening
[3] COVID-19 testing will be performed at screening and during scheduled visit as per investigator's discretion or if the patient presents symptoms
[4] At EOT, height will only be assessed in adolescent patients
[5] Including Adverse Events of Special Interest

8.1 Screening

After signing the study ICF, the screening assessments will be done within 1 to 35 days prior to Week 1 Day 1 (see Table 8-1 for list of assessments to be performed). The investigator will obtain consent / assent of participants and/or parents according to local procedures.

Re-screening of participants is only allowed **once** per participant if the participant was not enrolled in the treatment period before. In this case a new participant Number will be assigned via IRT and the participant will be identified with this new number for the rest of his/her participation in the study. If participant has been enrolled and treated, re-screening of participant is not allowed.

In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria. A new informed consent form must be signed only if there is an interruption in the participant's eligibility evaluation and the investigator chooses to re-screen the participant following screen failure. If a new informed consent form is signed, AEs and medical history will be assessed relative to the new informed consent date. Assessments from the initial screening can be used for re-screening if they fall within the screening window of 35 days before the first dose.

If the results from the central laboratory are partial or unavailable at time of the first infusion, local re-sampling is allowed from Day -14 on. Specifically, for platelet count test, local re-sampling is allowed at any time in case of clumping or other issues reported from the central laboratory.

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 participant. 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 participant will be considered a screen failure. For details of assessments, see Table 8-1.

8.1.1 Eligibility screening

Following IRT registration for screening, participant eligibility will be evaluated once all screening procedures are completed. The eligibility evaluation 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

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see SAE section for reporting details).

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition CRF.

8.2 Participant demographics/other baseline characteristics

Participant demographic characteristics, which include age, gender, self-identified race and ethnicity, will be collected.

Background medical information, including Sickle Cell and VOC History, prior use of HU/HC and reason for discontinuation (as applicable), ECG, ECOG/Karnofsky performance status, relevant and current medical history will also be collected.

Other baseline characteristics and assessments performed at screening for eligibility are detailed in Table 8-1.

8.3 Efficacy

Efficacy is not measured in this safety study.

8.4 Safety

Safety will be monitored by assessing physical examinations, vital signs, ECG, laboratory assessments including hematology, chemistry, coagulation, urinalysis, immunogenicity as well as by evaluation of adverse events as collected per schedule on Table 8-1.

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

Table 8-2 Assessment & 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 only at Screening. An abbreviated (short) physical exam will be performed at all remaining visits and includes the examination of general appearance and vital signs, as needed based on observed signs or reported symptoms. Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the participant's electronic Case Report Form (eCRF). Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the participant's eCRF.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, respiratory rate and body temperature. Vital sign will be performed at screening, at all visits for which there is a scheduled investigational treatment infusion, at EOT and also at Follow up visit (last infusion + 105 days).
Height and weight	Height will be measured at screening both in adults and adolescents and end of treatment for adolescents only. Body weight (in indoor clothing, but without shoes) will be measured at screening, at all visits for which there is a scheduled investigational treatment infusion (for dosing) and at end of treatment visit.

8.4.1 Laboratory evaluations

Clinical laboratory analyses are to be performed centrally, unless otherwise mentioned in the schedule of assessments or in Table 8-3. Novartis must be provided with a copy of the central laboratory's certification, 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.

If at any time a participant has laboratory parameters obtained from a different (local) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory.

The investigator is responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance.

For assessment of participants' eligibility to the study, laboratory results from the central laboratory will be used. If the results from the central laboratory are partial or unavailable at time of the first infusion, local re-sampling from Day -14 is allowed.

Specifically, for platelet count test, local re-sampling is allowed at any time in case of clumping (see Section 4.5) or other issues reported from the central laboratory. In such a case, eligibility may be based on the results from the local laboratory.

The results of the local laboratory will need to be recorded in the local lab eCRF if local tests are performed during the scheduled visits (or in the unscheduled local lab eCRF if performed during unscheduled visit).

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 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.

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 version 5. Additional analyses are left to the discretion of the investigator.

Table 8-3 Clinical laboratory parameters collection plan

Test Category*	Test Name**
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Reticulocytes (%), Platelets**, Red blood cells, White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea***, Uric Acid, Glucose (fasting) At Screening only and when medically indicated: Total Cholesterol, LDL, HDL, Total Protein, Triglycerides; Glucose in fasting state.
Urinalysis	Macroscopic Panel (Dipstick) will be done locally: Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, albumin, Specific Gravity, Urobilinogen Microscopic Panel: Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells performed, if a positive dipstick
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Hepatitis markers	HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR (At Screening only)
Additional tests	HIV Ab (at Screening only), COVID-19 testing (PCR)****
Pregnancy Test	Serum pregnancy test (at Screening, EOT and follow-up visit only), urine pregnancy test (before each infusion) will be done locally.

* At the discretion of the Investigator, safety laboratory tests can be performed locally before dosing (i.e, the day before or on the same dosing day).

**Local clinical laboratory collection only where specified. For platelet count test, local re-sampling is allowed at any time in case of clumping or other issues reported from the central laboratory.
*** Either BUN or Urea test to be performed. It will be defined in the Laboratory manual.
**** During the COVID-19 pandemic, if a participant experiences symptoms indicative of COVID-19 infection, viral testing for COVID-19 is recommended as per local guidance/practice.

8.4.2 Electrocardiogram (ECG)

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 locally conducted as outlined. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

Table 8-4 ECG collection plan

Visit	Time	ECG Type
Screening (Day -35 to Day -1)	Anytime	Triplicate 12 Lead

Visit	Time	ECG Type
Week 51 Day 1 (Last Infusion Visit)	Pre-dose (before infusion)	Triplicate 12 Lead
Safety Follow Up Visit	Anytime	Triplicate 12 Lead
Unscheduled with clinically significant finding	Anytime	Triplicate 12 Lead

Additional, unscheduled ECGs may be done at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. The mean result of the ECG analysis will be entered into the study database and used for AE reporting.

Clinically significant ECG abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

8.4.3 Pregnancy and assessments of fertility

All female participants of childbearing potential and premenopausal who are not surgically sterile must perform serum hCG pregnancy testing at screening in order to confirm study eligibility. Additional pregnancy testing might be performed per local requirements.

Serum pregnancy testing is required at screening, at the EOT visit, and at the follow up visit. During the study, urine pregnancy testing will be performed locally prior to each dosing. A positive urine pregnancy test needs to be confirmed with a serum hCG test. If confirmed, the participant must be discontinued from study treatment and the pregnancy reported to Novartis within 24 hour (see Section 10.1.4).

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

Assessment of fertility:

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy

2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.5 Additional assessments

8.5.1 Pharmacokinetics

Immunogenicity (IG) samples will be collected along with pre-dose (Ctrough) pharmacokinetic (PK) samples at the visits defined in the assessment schedule (Table 8-1). PK data is collected to support the evaluation of IG results.

Follow instructions outlined in the [CSEG101A2403 Laboratory Manual] regarding sample collection, numbering, processing and shipment.

The number of samples/blood draws collected will not exceed those stated in the protocol.

8.5.1.1 Pharmacokinetics and Immunogenicity blood collection and handling

At specified time points described in Table 8-5, blood samples will be taken by either direct venipuncture or through an indwelling cannula or port.

Each serum sample should be labeled with the appropriate study, center, and participant numbers, as well as the sequential PK/IG samples and PK/IG collection number with a unique sample number. The actual collection date and time of each sample will be entered on the PK/IG blood collection eCRF pages.

Refer to the [CSEG101A2403 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of IG and PK samples.

Table 8-5 Pharmacokinetic and Immunogenicity blood collection log

Week / Day	Scheduled Time Point	Dose reference ID	PK Sample No	IG Sample No	Sample Volume
Week 1 Day 1	Pre-dose	1	1	101	5.0 mL
Week 3 Day 1	Pre-dose	2	2	102	5.0 mL
Week 15 Day 1	Pre-dose	3	3	103	5.0 mL
Week 27 Day 1	Pre-dose	4	4	104	5.0 mL
Week 39 Day 1	Pre-dose	5	5	105	5.0 mL
Week 51 Day 1	Pre-dose	6	6	106	5.0 mL
Safety Follow Up[a]	-	601	7	107	5.0 mL
Unscheduled[b]	-	-	1001+	2001+	5.0 mL
Total					35 mL

Pre-dose is within 24 hours before dose administration
[a] the actual date and time of administration of the previous dose of study medication should also be recorded with Dose Reference ID 1 for 601
[b] unscheduled samples may be obtained as appropriate to support safety assessment

8.5.2 Sickle cell VOC event

VOC is defined as a pain crisis (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. Acute chest syndrome (ACS), priapism and hepatic or splenic sequestration and as per investigator's discretion will be considered VOC in this study.

Only VOC leading to healthcare visit will be collected and this is defined as a VOC with any visit to a medical facility such as an emergency room, hospital and/or office visit, which includes pain management of that VOC in situ.

VOCs occurring within 7 days following the documented resolution of a crisis event will be counted as part of the prior crisis, and the date for end of VOC will subsequently be revised.

In certain cases, due to the anatomic location and/or characteristics of the event, the investigator may consider it as new VOC, in which case it will be reported as separate event in the eCRF.

Associated conditions in SCD (e.g., intermittent or chronic pain due to ankle/leg ulcers, aseptic necrosis of bone or gout) should not be considered a VOC event. Similarly, complications such as pulmonary, cardiac, or renal failure are not themselves to be considered crises. If such events precipitate VOC, the event will be documented separately.

For each visit to a medical facility for a pain episode thought to be a VOC, the following information must be documented in the eCRF: diagnostic evaluation for the episode, participant treatment, duration of the crisis, and outcome. For participants who are treated at medical facilities other than the study site, summary documents will need to be obtained.

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

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

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

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

The investigator must discontinue study treatment for a given participant if he/she believes that continuation would be detrimental to the participant's well-being.

In addition to mandatory discontinuation reasons for study treatment listed in Section 6.5section_6_5_1, study treatment **must** also be discontinued under the following circumstances:

- Pregnancy
- Lactation
- Participant/Guardian decision
- Unsatisfactory therapeutic effect as per Investigator decision

- Grade 4 AE and dose interruptions of investigational treatment due to toxicity (see Section 6.5section_6_5_1)
- Use of prohibited medication (see Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the participant

Following the treatment discontinuation, participants will perform an End of Treatment visit. Permanent treatment discontinuation is mandatory for specific events indicated as indicated in Table 6-2. All participants must be followed up for adverse events and serious adverse events for 105 days following the last dose of crizanlizumab.

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

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued 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 participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of

telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination could be the following:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant'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 participant finishes their Study Completion visit 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.

All treated participants should have a safety follow-up visit conducted 105 days (15 weeks) after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

Novartis will make every effort to supply crizanlizumab (SEG101) to participants who may benefit from continued treatment as per the Investigator's opinion; safety will be monitored and reported to Health Authorities per regulatory requirements.

10 Safety monitoring and reporting

During the COVID-19 pandemic that limits or prevents on-site study visits regular phone calls will occur for safety monitoring and discussion of the participant´s health status until the participant 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 adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant 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 participant and identifying adverse events.

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

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

Adverse events must be recorded 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. The Common Terminology Criteria (CTC) AE grade (version 5). Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.
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) 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 participant.
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
5. Action taken regarding with study treatment.

   All adverse events must be treated appropriately. Treatment may include one or more of the following:

   - Dose not changed
   - Drug interrupted/withdrawn

6. Its outcome (not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF 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 participant.

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 for at least 105 days following the last dose of study treatment.

Once an adverse event 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.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events 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 participant with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [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 participant 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 participant'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 participant 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 participant 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 emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new 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 serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 105 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

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 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 participant continued or withdrew from study participation

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) 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 safety follow-up period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

Section 10.3 describes protocol exempted AEs and SAEs.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy 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.

If the pregnancy results in a live birth, the baby will have regular check-ups and the Study Doctor will need to know the outcomes of these check-ups until one year after the baby was due to be born.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the crizanlizumab (SEG101) 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, participant 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 CRF irrespective of whether or not associated with an AE/SAE and reported 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 CRF (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 (Section 10.1.1 and Section 10.1.2).

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 (DILI) cases.

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

10.2.2 Renal safety monitoring

Not applicable.

10.3 Protocol Exempt AEs & SAEs

Protocol Exempt AEs & SAEs are implemented in the SEG101 program. VOCs must be reported on the VOC page in the eCRF. AEs and SAEs involving VOCs 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. Procedures which are directly related to the VOC, e.g. ventilation of a participant with acute chest syndrome are considered part of the VOC and will not be reported as AE/SAEs but entered in the eCRF-page "concomitant non-drug therapies/procedures". 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.

The events in Section 8.5.2 are the VOCs that will not be reported as AEs/SAEs. However, in case a VOC event is suspected to be related to study treatment, and/or resulting in a fatal outcome, it will be reported also as AE/SAE in addition to the VOC eCRF page.

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

The investigator/designee is responsible for assuring that the data 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 participant 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 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 (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, enrollment, screen failures and study completion, as well as data about all study treatment (s) dispensed to the participant 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. Any changes to the database after that time can only be made after written agreement by Novartis development management.

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

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 participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, 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 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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The primary 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

Full Analysis set:

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of study treatment.

Safety Set:

The Safety Set includes all participants who received at least one dose of study treatment.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term.

The number of VOCs leading to healthcare visit will be summarized descriptively.

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, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to crizanlizumab as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

The number of participants with dose adjustments (interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system.

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary endpoint is the frequency, severity and causality of SAEs over the treatment period.

12.4.2 Statistical model, hypothesis, and method of analysis

The number and proportion of patients with at least one SAE will be presented along with the 2-sided 95% confidence interval (CI). SAEs will be summarized by number and percentage of participants having at least one SAE in each primary system organ class (SOC) and for each preferred term. SAE's will be summarized by relationship, leading to treatment discontinuation, leading to dose interruption and leading to fatal outcome.

12.5 Analysis of secondary endpoints/estimands

The secondary endpoint is the frequency, severity and causality of AEs as well as the assessment of labs, vital signs, ECGs and immunogenicity.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Not applicable.

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, urinalysis, coagulation, measurement of vital signs, ECG evaluation and physical examination.

For all safety analyses, the safety set will be used.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 105 days after last dose of study medication
3. Post-treatment period: starting at day 105+1 after last dose of study medication

Adverse events

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

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

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

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

All AEs, deaths, and serious adverse events (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.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per NCI 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.

CTCAE 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 version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings/summaries will be generated separately for hematology, biochemistry, urinalysis (macroscopic only), coagulation tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE version 5.0:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 5.0:

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

In addition to the above mentioned tables and listings, other exploratory analyses, for example, figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

Specific analyses to assess the impact of the liver function tests will be performed and described in the analysis plan.

Vital signs

All vital signs data will be listed by patient and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12-Lead ECG

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

All ECG data will be listed by patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Immunogenicity and Pharmacokinetics

All immunogenicity results and pre-dose PK will be listed by participant and visit/time.

12.6 Analysis of exploratory endpoints

Not applicable.

12.7 Interim analyses

No interim analysis is planned for this trial.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

This is a descriptive study and no hypothesis testing will be conducted. However the primary endpoint which is the proportion of patients reporting an SAE over the treatment period, will be presented with a 2-sided 95% CI.

In the SUSTAIN study ([CSEG101A2201]), the proportion of patients reporting at least one SAE over the treatment period on Crizanlizumab 5mg/kg was 26%.

Assuming the percentage of patients with at least one serious adverse event in this study in India should be approximately in the range of values previously observed, the half width of the confidence interval is calculated for potential observed proportions of 15, 25 and 35%.

With a sample size of 140 patients, the half-width of the confidence interval would vary from +/-5.9 to +/-7.9 if the proportion of patients with SAEs remains between 15 and 35%. This precision is considered appropriate to estimate with enough reliably the safety profile of crizanlizumab in India. The sample size calculation is done in EAST version 6.4.

Table 12-1 Confidence intervals (95%) for different proportions of SAE

Sample Size	Assumed proportion of SAE	Half width of 95% 2-sided CI	Lower 95% 2-sided CI	Upper 95% 2-sided CI
140	0.15	0.059	0.091	0.209
140	0.25	0.072	0.178	0.322
140	0.35	0.079	0.271	0.429

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 Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant 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 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 (defined as last patient last visit) 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 Standard Operating Procedures 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 participants 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.

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 participant 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 participant 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.

15 References

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16 Appendices

Not applicable.