NOVARTIS

Clinical Development

SEG101, Crizanlizumab

Oncology Clinical Trial Protocol

CSEG101A2202 / NCT03264989

A phase 2, Multicenter, Open-Label Study to Assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/Hydroxycarbamide, in Sickle Cell Patients with Vaso-Occlusive Crisis

Document type	Amended Protocol Version
EUDRACT number	Not applicable
Version number	01 (Amended Protocol Version) Clean
Development phase	II
Document status	Final
Release date	04-Jun-2018

Template version 6-Apr-2017

[redacted]

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List of abbreviations

ACS	Acute Chest Syndrome
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase / glutamic pyruvic transaminase /GPT
AST	Aspartate aminotransferase / glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BSA	Body Surface Area
CDP	Clinical Development Plan
CRD	Chronic Renal Disease
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
CMO&PS	Chief Medical Office and Patient Safety
ECG	Electrocardiogram
ER	Emergency Room
FAS	Full Analysis Set
FMI	Final Market Image
Hb	Hemoglobin
HbA	Hemoglobin A
HbS	Human hemoglobin S (sickle cell hemoglobin)
HbSC	Heterozygous sickle Hemoglobin C disease (hemoglobin SC disease)
HbS β	Heterozygotes with one copy of the HbS gene and a β-thalassemia variant (β^0 or β^+)
HbSS	homozygous sickle cell disease (hemoglobin SS disease)
HU/HC	Hydroxyurea/Hydroxycarbamide
GFR	Glomerular Filtration Rate
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MDRD-GFR	Modification of Diet in Renal Disease-Glomerular Filtration Rate

[redacted]

NSAID(s)	Non-Steroidal Anti-Inflammatory Drug(s)
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PDS	Pharmacodynamics Analysis Set
PHI	Protected Health Information
PK	Pharmacokinetics
PKPDS	Pharmacokinetic-Pharmacodynamics Analysis Set
popPK	Population PK
PSGL-1	P-selectin glycoprotein ligand-1
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RR	Risk Ratio
SAE	Serious Adverse Event
SCD	Sickle Cell Disease
SCPC	Sickle Cell-related Pain Crises
SOP	Standard Operating Procedure
VOC	Vaso-Occlusive Crisis

[redacted]

Glossary of terms

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 subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Perpetrator drug	Drug which affects the pharmacokinetics of the other drug
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
SEG101	Novartis supply of crizanlizumab
SelG1	Reprixys supply of crizanlizumab
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

[redacted]

Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact
Withdrawal of study consent	Withdrawal of study consent: Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol summary:

Title	A phase 2, Multicenter, Open-Label Study to Assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/Hydroxycarbamide, in Sickle Cell Patients with Vaso-Occlusive Crisis
Brief title	Pharmacokinetics and pharmacodynamics study of SEG101 (crizanlizumab) in Sickle Cell Disease (SCD) patients with Vaso-Occlusive Crisis (VOC)
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Crizanlizumab is a humanized monoclonal antibody that binds P-selectin and was previously found to reduce the median annualized rate of VOC at 5 mg/kg by 45.3% compared to placebo. Clinical and toxicological studies performed to date for crizanlizumab were conducted using Reprixys material (SelG1 mAb). To ensure supply of future clinical studies as well as commercial demand, Novartis has optimized the production of crizanlizumab. The Novartis material (SEG101 mAb) drug substance (DS) and drug product (DP) will be manufactured at Novartis sites. The change in manufacturing cell line is not expected to impact the bioavailability or activity of the compound. The purpose of the CSEG101A2202 study is to characterize the PK and PD of SEG101 and to evaluate the safety and efficacy of SEG101.
Primary Objective(s) and Key Secondary Objective	To characterize PK of crizanlizumab at 5.0 mg/kg in SCD patients. To characterize PD (P-selectin inhibition) of crizanlizumab at 5.0 mg/kg in SCD patients
Secondary Objectives	To assess the efficacy of crizanlizumab in SCD patients in terms of annualized rate of VOC events leading to healthcare visit in clinic/ER/hospital, annualized rate of VOC events treated at home, annualized rate of hospitalizations and ER visits, annualized rate of ER/hospitalization, annualized rate of each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism), annualized rate of VOC events. To assess the safety and tolerability of crizanlizumab in terms of the number, seriousness, severity, and causality assessments of treatment emergent adverse events and other safety data as considered appropriate and absolute change from baseline in hemoglobin
Study design	Open-label, single arm study of crizanlizumab therapy in SCD patients.
Population	55 male and female SCD patients ages 16-70 years who experienced at least 1 VOC over the preceding 12 months, and who are not planning to take HU/HC during the trial or are receiving stable treatment with HU/HC.
Inclusion criteria	• Male and non-pregnant female patients 16-70 years of age (inclusive) • Confirmed diagnosis of sickle cell disease by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) [performed locally]. All sickle cell disease genotypes are eligible. • Experienced at least 1 VOC within the preceding 12 months prior to Screening, as determined by medical history. • If receiving HU/HC or erythropoietin stimulating agent, must have been receiving the drug for at least 6 months prior to Screening

[redacted]

	• Hemoglobin ≥4.0 g/dL. Absolute neutrophil count $\geq$1.0 x 10^9/L and platelet count $\geq$75 x 10^9/L
	• Adequate renal and hepatic function as defined:
	  • GFR ≥45 mL/min/1.73 m^2 calculated by CKD-EPI
	  • ALT ≤3 x ULN
	  • Direct (conjugated) bilirubin ≤2 x ULN
	• ECOG performance status ≤2
	• Written informed consent prior to any screening procedures

Exclusion criteria	• History of stem cell transplant. • Acute VOC ending within 7 days of W1D1 dosing • Received blood products within 30 days prior to W1D1 dosing. • Participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) • History of severe hypersensitivity reactions to other monoclonal antibodies • Received a monoclonal antibody or immunoglobulin-based agent within 1 year of Screening, or has documented immunogenicity to a prior biologic. • Received active treatment on another investigational trial within 30 days (or 5 half-lives of that agent, whichever is greater) prior to Screening • Significant active infection or immune deficiency (including chronic use of immunosuppressive drugs) in the opinion of the investigator • Resting QTcF ≥470 msec at pretreatment (baseline) or other cardiac or cardiac repolarization abnormality
Investigational and reference therapy	SEG101 (crizanlizumab) drug at a dose of 5.0 mg/kg (or 7.5 mg/kg for exploratory group) by IV infusion over 30 min on week 1 day 1, week 3 day 1, and then day 1 of every 4-week cycle.
Efficacy assessments	-VOCs leading to healthcare visit in clinic/ER/hospital -VOCs treated at home, based on documentation by health care provider following telephone contact with patient -Each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism) -Hospitalizations and ER visits (both overall and VOC-related)

[redacted]

Safety assessments	Safety will be monitored by assessing the following parameters: -Vital signs -Physical exam -ECG in triplicates at all PK assessment timepoints [central review] -Hematology, blood chemistry, coagulation and urinalysis (additional laboratory tests will be performed at the investigator's discretion for safety measures in the event of an adverse event) -Pregnancy [redacted] -Monitoring of AEs/SAEs
[redacted]	
Data analysis	PK parameters including AUC and Cmax will be derived from individual concentration-time profiles after the first dose and the 5th dose. The inter-subject variations and CV% will be presented for the primary PK parameters. The point estimate and the corresponding two-sided 90% confidence interval (CI) for the mean of the log-transformed primary PK parameters after single dose and multiple doses will be derived respectively. The point estimate and CI will be anti-log transformed to obtain the point estimate and the 90% confidence interval for the geometric mean on the original scale. The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented for all PK parameters except Tmax, where only n, median, minimum and maximum will be presented. Descriptive statistics for crizanlizumab concentration will be presented at each scheduled timepoint. PD-AUCd15 and PD-AUCd29 will be derived from the %P-selectin inhibition time profiles of week 1 and week 15, respectively. The point estimate and the corresponding two-sided 90% CI for the mean of the log-transformed PD-AUC after single dose and multiple doses will also be provided. The point estimate and CI will be anti-log transformed to obtain the point estimate and the 90% confidence interval for the geometric mean on the original scale. Descriptive statistics for PD inhibition will be presented at each scheduled timepoint.
Key words	Sickle cell disease, sickle cell anemia, vaso-occlusive crisis, P-selectin

[redacted]

Amendment 01 (04-Jun-2018)

Amendment rationale

The study is currently open for enrollment with 21 subjects enrolled to date.

Due to the ongoing high unmet medical need for prevention of VOC in SCD, particularly for patients age <18 years old, and the unexpected delay in start of the SEG101 phase 2 (CSEG101B2201) trial for ages 6 months to 18 years, the decision was made to expand the inclusion age in CSEG101A2202 to include 16 and 17 year old subjects. This is based on the well-established and widely-accepted view that there is no meaningful difference in PK between adolescents (here ages 16-<18 years) and adults 18 years and older. Monoclonal antibodies are distributed within the vascular and extracellular spaces by mechanisms dominated by convection, and predominately catabolized by lysosomal enzymes to small peptides and amino acids. It is unlikely that these (the vascular and extracellular fraction in the body and enzyme activity) differ in age 16 vs. 18, therefore PK is expected to be similar between age 16 vs. 18.

Participating investigators have provided feedback after enrolling their initial patients to the study. They suggested the protocol inclusion and exclusion criteria be examined and modified regarding the timing of prior VOCs and historical testing information as well as current treatment be clarified.

This amendment also clarifies that the VOC events should not be reported as adverse events.

Further review of the secondary endpoints led to the changes from the number of efficacy related endpoints to the annualized (rates) – this accounts for any early subject withdrawal by setting one year as a standard time period.

Additional PK samples have been added to align with the IG sample collection timelines. Additional safety information has led to the adjustment of the dose modification guidance for this compound, including the removal of the dosing modification requirements for hypertension, the addition of dosing modification guidelines for QTc prolongation, as well the correction of editorial and typographical errors.

Changes to the protocol

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

- Throughout: Typographical and grammatical errors addressed.
- Throughout: Removed references to “adult” in protocol title, objectives, study design, endpoints.
- Abbreviations: Added NSAID
- Glossary: Added definitions for personal data and withdrawal of study consent. Removed supportive treatment from glossary.
- Section 2.3: Clarified the two doses and the future Phase III trial design.
- Section 2.6: Removed pre-clinical information.

- Table 3.1: Revised primary [redacted] objective from trough to pre-dose concentrations. Revised the secondary [redacted] endpoints from number, to annualized (rates). [redacted]
- Section 4.1: Clarified HU/HC dosing requirements. Removed requirement to be off HU/HC for 6 months if taking HU/HC at time of enrollment. Changed screening window from 28 to 35 days. Updated Figure 4.1 to reflect amendment changes.
- Section 4.2: Added provision for additional ad hoc analyses. Revised interim analysis from will be, to may be performed. Revised the potential impact of the interim analysis.
- Section 4.3: Clarified end of study participation criteria
- Section 5.1: Revised patient population to include 16-17 year olds in the population
- Section 5.2: Changed inclusion age to 16 from 18 years in inclusion criteria #1
- Section 5.2: Clarified definitions for VOC treatments in inclusion criteria #3
- Section 5.2: Removed inclusion criteria #5 – chest X-ray
- Section 5.3: Revised exclusion #2 to reflect excluding VOCs ending within 7 days prior to first dose, instead of 15 days prior to screening. Removed Exclusion criteria #13 requiring male contraception due to monoclonal antibody pregnancy guidance. Revised exclusion criteria #15 to allow silent infarct only present on imaging. Revised exclusion criteria #19 to allow for well controlled HIV positive subjects to be included.
- Section 6.3.1: Revised the missed doses requirement for discontinuation to reflect 2 consecutive missed for any reason within a 10 week period.
- Table 6.2: Clarified total bilirubin to be total bilirubin (direct [conjugated] and/or total). Deleted hypertension dose modification requirements as per the change in program standard language.
- Section 6.3.1.2: Added section of dose adjustments for QTcF prolongation.
- Section 7.1: Changed screening window from 28 to 35 days.
- Table 7-1: Changed screening window to 35 days. Removed visit numbers. Updated protocol sections. Changed location of pregnancy test results from Database to Source. For drug screen, clarified which results will be captured in source verses database. Updated Chest X-ray [redacted] to allow for procedure within 3 months of first dose. [redacted]
- Section 7.1.2: Revised re-screening numbering per the new database standards. Changed screening window to 35 days. Removed sentence regarding ICF timing for re-screening.
- Section 7.1.4: Revised to clarify the timing of the full PK/PD profiles if a dose is interrupted.
- Section 7.1.5.1: Deleted replacement policy section as Not Applicable.
- Section 7.1.6: Update withdrawal of consent section to reflect current Novartis legal language

[redacted]

- Section 7.2.1: Clarified language regarding end date for VOC based on pain medication management. Updated definition of ACS based on symptoms and end of priapism to 2 hours from 1 hour. Removed requirement to hold dosing until VOC resolves. Added sentence "VOC is not a known contra-indication, but dosing during a crisis should be at investigator's discretion". Clarified medications for VOC definition.
- Table 7-2: Updated table to add optional PK/PD samples around transfusion. Added optional PK, soluble P-selectin and PD samples at onset and resolution of VOC events.
- Section 7.2.2.5: Clarified laboratory testing should be done centrally unless otherwise noted.
- Table 7-3: Updated to reflect which are local and which are central laboratory tests.
- Section 7.2.2.2.5 Added "if central laboratory results are unevaluable or inconclusive" as a criteria to draw local labs
- Section 7.2.2.5.2: Revised to note that blood alcohol test will be performed locally
- Section 7.2.2.5.3: Revised to note that the macroscopic urinalysis will be done locally and the microscopic will be done centrally.
- Section 7.2.2.5.5.: Revised to reflect the serum pregnancy testing will be performed centrally and the urine pregnancy testing will be performed locally.
- Section 7.2.2.5.6: Added section regarding the Hepatitis markers testing.
- [redacted]
- [redacted] based on tubes to be used.
- Table 7.5: Added PK samples 33-38 (Weeks 75, 99, 123,147, 171). Added Follow up Phase time point and samples for PK and IG. Updated number of doses needed to reach steady state if dose(s) missed.
- Section 8.1.1.: Removed sentence about VOC not being reported as AEs.
- Section 8.1.1.1 and Table 8-1: Added section on Protocol Exempt AEs and SAEs.
- Section 8.2.1: clarified VOCs not SAEs
- Section 9.3: Added missing part of sentence for reconciliation of information.
- Section 10: Added clarification that 5.0 mg/kg enrollment will end at 27 evaluable, or 45 total patients, whichever occurs first.
- Section 10.1.3: Added clarification regarding the timing of the full PK/PD profiles if a dose is interrupted.
- Section 10.1.4.1: Added clarification regarding the timing of the full PK/PD profiles if a dose is interrupted.
- Section 10.5.2: Changed secondary efficacy objectives from number of to annualized rate of VOC events and hospitalizations.

[redacted]

[redacted]

- Section 10.7: Added provision for additional ad hoc analyses.
- Section 13: Updated the references

IRBs/IECs

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

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

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

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Sickle cell disease (SCD) is a rare autosomal recessive blood disorder caused by a single missense mutation (Glu6Val) in the β-globin gene that renders the mutant hemoglobin less soluble and prone to polymerization upon deoxygenation. The polymerization of hemoglobin causes deformation of the erythrocyte to give the cell a "sickle" shape (Bookchin 1996), and leads to chronic hemolysis, anemia, and vaso-occlusion (NHLBI, The Management of Sickle Cell Disease. NIH Publication No.022117; Wethers 2000). SCD is the most common single gene disorder in African Americans, affecting approximately 1 in 375-600 persons of African ancestry (Clinical Practice Guideline No. 6. April 1993; Nietert 2002). Sickle cell conditions are also common among people of Mediterranean countries, Africa, the Caribbean and parts of South and Central America (Clinical Practice Guideline No. 6. April 1993; Nietert 2002).

In SCD, lysis of sickle red cells, cell membrane damage and oxidative stress, repeated ischemic damage, and microvasculature injury are due to the adhesive interactions between sickle red cells and the endothelium, which culminate in a pro-inflammatory environment (Embury 2004; Chiang 2005). In this environment of chronic vascular inflammation, the adherence of leukocytes, platelets and sickle red cells to activated blood vessel endothelium and to each other is believed to be the primary cause of microvasculature blockage and vaso-occlusive crisis (VOC), the clinical hallmark of SCD, typically associated with intense pain. Additional factors such as the rigidity of sickle red cells, increased blood viscosity, and local vasoconstriction have also been identified as potentially contributing to the vaso-occlusion process. VOC includes pain crises (defined as an acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids or parenteral NSAIDs) as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration (Maitre et al. 2000; Vichinsky et al. 2000). VOC accounts for over 90% of hospital admissions in adult SCD patients (Matsui et al. 2001; Chiang 2005; Okpala 2006).

SCD patients also suffer from cerebrovascular complications, ranging from clinically evident acute stroke to transient silent ischemic infarct (Platt 2006). Other chronic complications include functional asplenia, leaving patients more susceptible to infection, (Clinical Practice Guideline No. 6. April 1993), bone growth retardation and avascular necrosis renal dysfunction (Saborio 1999), and issues of the biliary tree (gallstones, congestion), eyes (retinopathy) (Charache 1996), and soft tissue (leg ulcers) (Ashley-Koch 2000; Gladwin et al., 2004; Gladwin 2005). Chronic pain and opioid abuse are also common (Smith 1996). As a result, there is an approximately 20 to 30 year reduction in life expectancy in SCD patients (Platt et al. 1994).

Hemoglobin values for SCD patients vary, but typically range from 6 to 10 g/dL, but some patients can live with a baseline hemoglobin of 4 g/dL or lower. Chronic hemolysis results in other abnormal labs, including reticulocytosis, low haptoglobin, and increased free hemoglobin, LDH, indirect bilirubin (and, by extension, total bilirubin). In young SCD patients, glomerular filtration rate (GFR) is substantially increased (hyperfiltration: MDRD-GFR >130 in women, >140 ml/min per 1.73 m2 in men) but tends to decrease progressively with time, and 4-5% of these patients in the US develop stage 5 chronic renal disease (CRD) (Hirschberg 2010). SCD

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patients are also more susceptible to parvovirus B19 infection which can arrest erythropoiesis and lead to aplastic crisis (Heegaard 2002).

SCD has three common variants: homozygous SCD (hemoglobin SS disease), doubly heterozygous sickle hemoglobin C disease (hemoglobin SC disease) and the sickle β-thalassemia. The most common and severe form of the disease occurs in individuals who inherit two copies of the HbS variant (HbSS) and the primary hemoglobin in their red blood cells is sickle hemoglobin. Other individuals can be affected as compound heterozygotes with one copy of the HbS gene and one or more additional mutations, resulting in varying severities of the disease. HbSC results in a mild-to-moderate form of the disease. HbS β-thalassemia variants (β^0 or β^+) result in a range of clinical severities: HbSβ^0 is a severe form, whereas HbSβ^+ can be moderate or mild based on the contribution of each variant to the total hemoglobin of the patient. Other more rare variants can result if in addition to the HbS gene, another abnormal hemoglobin is inherited from the other parent, such as D, G or O-Arab. The sickle red cells gene is most commonly present in individuals heterozygous for HbS and HbA. These individuals carry the sickle cell trait and are asymptomatic (Clinical Practice Guideline No. 6. April 1993; Nietert et al. 2002).

All individuals that are homozygous or compound heterozygous for HbS show some clinical manifestations of SCD. Clinical signs appear within the first 6 months of life but there is considerable variability in severity (Gill et al. 1995). Disease severity is thought to depend on a complex interaction of genetic, rheologic and hematologic factors, as well as microvascular and endothelial factors. Therefore, despite the capacity to determine genotype, the ability to predict disease course from birth is limited (Thomas 1997). The frequency of VOC and pain severity varies considerably among patients and in the same patient over time. Moreover, a recent study (PiSCES) evaluating health related quality of life issues in SCD patients indicated that VOC might be significantly underreported among SCD patients (McClish et al. 2005).

Treatment for SCD includes supportive care for VOC. The two most common symptomatic treatments are blood transfusions and analgesics. Blood transfusions both increase hemoglobin level and lower the proportion of sickled cells, thereby increasing oxygen delivery to tissues and potentially reducing pain. Severe pain is often treated with narcotics but their use is controversial due to concerns of narcotic addiction and tolerance. Other complications of narcotic use are drug-seeking behavior, sedation and respiratory depression. Oxygen management has been utilized to treat VOC, despite the lack of strong evidence supporting its effectiveness. Rehydration is also used during VOC with some apparent benefit (NHLBI, The Management of Sickle Cell Disease. NIH Publication No.022117; Yale 2000).

Preventative therapies for SCD include chronic red cell transfusion programs to reduce the incidence of stroke in high-risk patients, Hydroxyurea/Hydroxycarbamide (HU/HC, Droxia/Siklos) is approved for VOC. The mechanisms by which HU/HC produces its beneficial effects are uncertain but likely involve increasing hemoglobin F levels in RBCs, thereby decreasing the amount of hemoglobin S polymerization. Hydroxyurea is cytotoxic, myelosuppressive and teratogenic (Charache et al. 1995), and the long-term effects of hematologic toxicities, organ damage and carcinogenicity are currently unknown (NIH Consensus and State-of -the Science Statements 2008). L-glutamine was recently approved by the FDA to reduce the complications of sickle cell disease in adult and pediatric patients 5 years and older. Bone marrow transplantation may be considered and can be curative, but a limited

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number of patients are eligible, and this carries a high risk of morbidity and mortality (NHLBI The Management of Sickle Cell Disease. NIH Publication No.022117). Thus, SCD is a life-threatening disease with severe morbidities and represents a major unmet medical need.

The recognition that adherence of leukocytes, platelets and sickle red cells to blood vessel endothelium and to each other to 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. Under shear flow in the blood, leukocytes first tether and begin rolling on vascular endothelium, eventually adhering firmly and infiltrating into the underlying tissue (Springer 1995). Selectins interact with glycoconjugated ligands on leukocytes to initiate this process (McEver 1995; Vestweber 1999). Transient adhesion mediated by selectins is a prerequisite for firm adhesion mediated by integrin receptors and subsequent transendothelial migration of leukocytes. Three selectins have been identified: P-, E- and L-selectin. 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 1998). P-selectin is stored in Weibel-Palade bodies in endothelial cells that line blood vessels and in α-granules in platelets.

Extensive data have been published over the last decade that suggests a pivotal role for P-selectin in the pathophysiology of SCD (Matsui 2001). Much of this work has been conducted in mice engineered or altered to express human hemoglobin S (sickle cell hemoglobin) but not mouse β hemoglobin. These mice have a remarkably similar disease pathology and inflammatory profile to that observed in human SCD, including vaso-occlusion. Using these mice, investigators have demonstrated P-selectin interactions between the endothelium and sickled red blood cells, leukocytes, and platelets. Additional studies have demonstrated direct P-selectin-mediated binding of leukocytes with sickled red cells and platelets. All of these cell-cell interactions have been implicated in SCD vaso-occlusion. Further, blockade or genetic absence of P-selectin decreases or eliminates these cell-cell interactions and vaso-occlusion. Taken together, these studies establish P-selectin as a key mediator of vaso-occlusion in SCD.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of Crizanlizumab (SEG101)

Crizanlizumab (SEG101) is a humanized monoclonal antibody that binds P-selectin in humans and primates and blocks the interaction of P-selectin with its ligands. The compound was previously developed by Reprixys under the investigational drug code, SelG1, and subsequently became a legal entity of Novartis Pharmaceuticals on 18-Nov-2016.

1.2.1.1 Non-clinical experience

Crizanlizumab is administered intravenously (i.v.) with instantaneous absorption and assumed 100% bioavailability. As a humanized, monoclonal antibody, distribution is expected to be typical of endogenous human antibodies within the vascular and extracellular spaces by mechanisms dominated by convection, fluid-phase endocytosis, receptor-mediated endocytosis and their interaction with FcRn receptors (Heegaard 2002). Crizanlizumab contains only naturally occurring amino acids and has no known active metabolites. Human antibodies are

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predominately catabolized by lysosomal enzymes to small peptides and amino acids. The extent of catabolism is inversely proportional to FcRn receptor affinity (Dall'Acqua et al. 2002).

No specific studies have been conducted to evaluate specific pathways of crizanlizumab excretion. Due to its predicted molecular size of approximately 148 kDa, it is expected that crizanlizumab, like other immunoglobulins, is not eliminated by efficient filtration through the glomerulus in kidneys.

In addition to studies in rodents containing human sickled hemoglobin, other studies demonstrated that human sickled red cells adhere to human endothelial cells more frequently than normal red cells, and an anti-human P-selectin antibody inhibits this adherence (Matsui et al. 2001).

In experiments performed with the parental anti-human P-selectin antibody G1, the following data were generated: 1) G1 blocks the binding of human P-selectin to its ligand PSGL-1 (Geng et al. 1990) 2) G1 blocks leukocyte rolling and firm adhesion to human vascular endothelium under shear stress (Geng et al. 1990; Jones et al. 1993); 3) G1 effectively inhibits the interaction of neutrophils with stimulated platelets (Hamburger 1990); 4) G1 completely blocks the binding of human sickled red cells to human endothelium under flow (Wagner 2006); and 5) in mice expressing human but not mouse P-selectin, G1 blocks the rolling and adherence of leukocytes on mouse venules and can reverse pre-established leukocyte adhesion (Liu et al. 2010).

In experiments performed to confirm that the humanized form of G1 (SelG1) shares identical specificity and function with parental G1, SelG1 was shown to 1) bind P-selectin with an near identical affinity to that of G1; 2) maintain the same species restriction pattern as G1; 3) have the same epitope recognition pattern as G1; 4) effectively block the binding of P-selectin to its receptor on human cells and; 5) retain the receptor/ligand dissociative property of G1.

Due to the species restriction of SelG1 binding, much of the data available to date have been obtained from rodent modeling using mice expressing human hemoglobin S (sickle cell hemoglobin) with surrogate antibodies that block mouse P-selectin or animals genetically deficient in P-selectin. Where possible, the SelG1 parental antibody G1 has been used in experimentation in which human P-selectin is present. In addition, confirmatory data with SelG1 were established.

In mice expressing human sickled hemoglobin (human β^S mice) the following data were generated: 1) an anti-mouse P-selectin antibody blocks leukocyte rolling (Kaul 2000); 2) vaso-occlusion is blocked in animals deficient in P-selectin (Frenette 2004); 3) platelet and leukocyte adhesion to vascular endothelium is absent in P-selectin deficient animals (Wood 2004); and 4) sickled red cell microvascular flow is increased and vaso-occlusion decreased with an anti-mouse P-selectin antibody (Embury et al. 2004).

Finally, SelG1 has been administered to nonhuman primates in a single-dose and two separate GLP multi-dose studies. Administration of SelG1 by bolus IV injection once every 4 weeks to cynomolgus monkeys for a total of seven doses was well tolerated at doses $\leq$ 25 mg/kg/dose; the no observed adverse effect level (NOAEL) is therefore 25 mg/kg/dose.

As SelG1 is specific to human and nonhuman primate P-selectin and in accordance with the ICH S6 Guidance, no genotoxicity or reproductive toxicology studies have been performed to date.

[redacted]

1.2.1.2 Clinical experience

Phase I Clinical Study (CSEG101A2101)

The objectives of this study (Reprixys study code: Se1G1-00003; Novartis study code: CSEG101A2101) were to evaluate the safety, PK, PD, and immunogenicity of intravenously administered SelG1 versus placebo in 27 healthy subjects at ascending dose levels (0.2, 0.5, 1.0, 5.0 mg/kg and 8.0 mg/kg).

Crizanlizumab concentrations slowly declined, with mean half-life ranging from 75.6 (at dose of 0.2 mg/kg) to 500 (at 5.0 mg/kg) hours. Therefore, clearance decreased with the increase in dose level: 88.6 mL/hr. (at 0.2 mg/kg) to 9.91 (at 5.0 mg/kg). Following two intravenous infusions of SelG1 at 8.0 mg/kg, the mean half-life was 363 hours, and the clearance was 3.86 mL/hr. For subjects receiving a single dose of crizanlizumab at 5.0 mg/kg, P-selectin inhibition was complete for at least 28 days with a mean crizanlizumab concentration on Day 28 of 19.9±3.8 μg/mL.

There were no infection-related AEs, changes in coagulation parameters, increased bleeding tendencies, or notable treatment-related changes in peripheral blood immunophenotyping. The immunogenicity data generated during the Phase I clinical trial indicate that no specific antibody response to SelG1 occurred in any subjects receiving up to 2 doses of drug.

Based on AEs, clinical laboratory evaluations, vital signs measurements, physical examinations, and ECG evaluations, administration of SelG1 was safe and well-tolerated in this group of healthy male and female subjects.

Phase II Clinical Study (SUSTAIN – CSEG101A2201)

The purpose of SUSTAIN (Reprixys study code: Se1G1-00005; Novartis study code: CSEG101A2201) study was to investigate the safety and tolerability of the humanized anti-P-selectin monoclonal antibody, crizanlizumab (SelG1), during chronic administration to SCD patients and to investigate the efficacy of crizanlizumab to affect the rate of sickle cell-related pain crises (SCPC) (also known as VOC leading to a healthcare visit) as well as a variety of other clinical endpoints, anemia- and hemolysis-related laboratory parameters, pharmacokinetics/pharmacodynamics (PK/PD), and patient reported outcomes.

This trial was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study to assess the safety and efficacy of crizanlizumab versus placebo in patients with SCD, both receiving and not receiving HU/HC. Crizanlizumab was administered at 2 different dose levels (2.5 mg/kg and 5.0 mg/kg). A total of 198 patients were randomized and included in the intent-to-treat (ITT) population, with 67 patients randomized to receive crizanlizumab at 5.0 mg/kg (5.0 mg/kg treatment arm), 66 patients to receive crizanlizumab at 2.5 mg/kg (2.5 mg/kg treatment arm), and 65 patients to receive placebo (placebo treatment arm).

The primary efficacy parameter was the assessment of the annual rate of VOC leading to a healthcare visit, defined as an acute episode of pain, for which there is with no other medically determined explanation cause than a vaso-occlusive event, which requires a medical facility (clinic, emergency room (ER), or hospital) visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Acute chest syndrome, hepatic sequestration, splenic sequestration and priapism events requiring a visit to a medical facility

[redacted]

were also considered VOC leading to a healthcare visit for analysis purposes. It was observed that treatment with 5.0 mg/kg crizanlizumab resulted in an annual rate of VOC leading to a healthcare visit that was 45.3% lower than the rate with placebo which was statistically significant (p = 0.010). The annual rate of VOC leading to a healthcare visit in the 2.5 mg/kg crizanlizumab treatment arm was compared with that of placebo, and although favorable (32.6% reduction with active treatment), it was not statistically significant (p = 0.180). In addition, in the 5.0 mg/kg crizanlizumab arm, numerical and clinically significant reductions in the annual rate of VOC leading to a healthcare visit were observed across important subgroups, including patients receiving concomitant HU (32.1%) and not receiving concomitant HU (50.0%), and in patients with the HbSS genotype (34.6%) and non-HbSS genotype (50.5%) (HbSC, HbSβ0-thalassemia, HbSβ+-thalassemia, and others). The median annual rate of days hospitalized was numerically reduced in the 5.0 mg/kg arm versus the placebo arm (4.00 versus 6.87, respectively); however this difference was not statistically significant. Treatment with crizanlizumab at 5.0 mg/kg was associated with longer median time to first VOC leading to a healthcare visit compared with placebo (4.07 versus 1.38 months, p = 0.001) and median time to second VOC leading to a healthcare visit compared to placebo (10.32 versus 5.09 months, p = 0.022).

Crizanlizumab was well tolerated. Adverse events that occurred in ≥5% of patients in an active dose group and were more than 2 times higher than placebo were: arthralgia, pruritus, vomiting, chest pain, diarrhea, fatigue, myalgia, musculoskeletal chest pain, abdominal pain, influenza and oropharyngeal pain. There were 5 deaths during the study (2 at 5.0 mg/kg, 1 at 2.5 mg/kg and 2 in the placebo group), and no deaths were deemed related to study drug. The proportion of subjects experiencing SAEs was 25.8% at 5.0 mg/kg, 32.8% at 2.5 mg/kg and 27.4% in the placebo group. Adverse events that occurred in 10% or more of the patients in either active treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia (5.0 mg/kg: 18.2% versus 2.5 mg/kg: 14.1% versus placebo: 8.1%), diarrhea (10.6% versus 7.8% versus 3.2%), pruritus (7.6% versus 10.9% versus 3.4%), vomiting (7.6% versus 10.9% versus 4.8%) and chest pain (1.5% versus 10.9% versus 1.6%). No patient developed anti-drug antibodies (ADA) against crizanlizumab during the course of the SUSTAIN study.

A sub analysis of risk ratio (RR [95% confidence intervals]; p-value) of infections found no evidence of association between crizanlizumab and infections. For this analysis, two subgroups were analyzed: infections and serious infections. The results show for infections a RR of 1.03 [0.82-1.29]: p=0.819; and for serious infections a RR of 1.07 [0.58-1.97]: p=0.820. The results suggest that the risk of infections and serious infections in crizanlizumab and placebo groups was similar.

Overall, treatment of patients with SCD with crizanlizumab at 5.0 mg/kg showed positive clinical activity as demonstrated by a decrease in the annual VOC leading to a healthcare visit rate compared with placebo. Treatment with crizanlizumab at 5.0 mg/kg was also found to be well tolerated.

[redacted]

2 Rationale

2.1 Study rationale and purpose

Clinical and toxicological studies performed to date for crizanlizumab were conducted using Reprixys material (SelG1 mAb). To ensure supply of future clinical studies as well as commercial demand, Novartis has optimized the production of crizanlizumab. The Novartis material (SEG101 mAb) drug substance (DS) and drug product (DP) will be manufactured at Novartis sites. *In vitro* characterization and primate PK experiments conducted with both mAbs did not reveal significant differences that would influence PK/PD results. Therefore, the change in cell line is not expected to impact the bioavailability or activity of the compound. The CSEG101A2202 study will be the first trial to administer crizanlizumab to SCD adultpatients.

The purpose of this study is to characterize the PK and PD of crizanlizumab and to evaluate the safety and efficacy of crizanlizumab in SCD patients.

2.2 Rationale for the study design

Study CSEG101A2202 is designed as a Phase II, multicenter, open-label study. The first 45 patients (to identify 27 evaluable patients) will be enrolled to the treatment group crizanlizumab 5.0 mg/kg to complete full PK and PD sampling at week 1 and week 15. In all patients, pre-dose PK and PD samples will also be collected prior to each dose. [redacted] Once the first 45 patients are enrolled, 10 additional patients will be enrolled to the exploratory treatment group and begin at 7.5 mg/kg of crizanlizumab.

The patients will undergo a screening period from Day -35 to Day -1 in order to enable the study center to conduct the required tests for eligibility. The first 45 patients will be enrolled to receive infusion doses of crizanlizumab 5.0 mg/kg (test) on the first day (Week 1 Day 1), Week 3 Day 1, and then day 1 of every 4-week cycle. No dose reductions are allowed in the study for patients assigned to 5.0 mg/kg dose. Patients will continue on study until 105 days after discontinuing drug or until receiving crizanlizumab commercially or through a different study or access program. Patients may need to stay at the study center for at least 24 hours following the first drug administration during which time blood samples for measurement of crizanlizumab will be collected, and then after the fifth dose (Week 15 Day 1). Patients will be discharged from the study site on Day 2 of Week 1 and Day 2 of Week 15 and will return on Week 1 Day 4, Week 2 Day 1, Week 3 Day 1, Week 7 Day 1, Week 11 Day 1, Week 15 Day 1 (patients to stay at study site for 24 hours as described above), Week 15 Day 4, Week 16 Day 1, Week 17 Day 1, Week 19 Day 1, and Day 1 of every 4 weeks for ambulatory visit for additional pharmacokinetic/pharmacodynamics and immunogenicity assessments and at 105 days after the last dose for the safety follow-up visit.

After 45 patients are enrolled at the 5.0 mg/kg dose, up to 10 additional patients (to identify 6 evaluable patients) will be enrolled to the exploratory treatment group of 7.5 mg/kg crizanlizumab. [redacted] The 10 patients will receive infusion doses of crizanlizumab at 7.5 mg/kg on the same schedule and with the same

[redacted]

administration requirements as for the 5.0 mg/kg group. [redacted]

2.3 Rationale for dose and regimen selection

Patients will receive crizanlizumab at a dose of 5.0 or 7.5 mg/kg by IV 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 initial dose every 4-weeks ± 3 days to ensure that steady-state serum concentrations of crizanlizumab are maintained to provide a consistent blockade of P-selectin throughout the study.

The SUSTAIN trial tested either 5.0 mg/kg or 2.5 mg/kg of SelG1 on this same dosing schedule and showed a statistically significant reduction in median annual rate of VOC leading to a healthcare visit in the 5.0 mg/kg dose group versus placebo, while the 2.5 mg/kg group did not have a statistically significant reduction. The overall safety was well-balanced across treatment and placebo groups (5.0 mg/kg: 86% AE and 26% SAE – 2.5 mg/kg: 88% AE and 33% SAE – placebo: 89% AE and 27% SAE) (Ataga 2016). The doses chosen for the SUSTAIN study were based on complete P-selectin inhibition of SelG1 in healthy subjects, as well as the acceptable safety experience observed with 5.0 mg/kg and 8.0 mg/kg dosing regimens during the Phase I safety study. As mentioned in Section 1.2.1.2, the phase I study (CSEG101A2101) found that a single dose of SelG1 at 5.0 mg/kg yielded at least 28 days of complete P-selectin inhibition.

[redacted]

2.4 Rationale for choice of combination

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Risks and benefits

Overall, treatment of SCD patients with crizanlizumab at 5.0 mg/kg demonstrated statistically significant, clinically meaningful, and robust efficacy results vs. placebo in reduction of annual rate of sickle cell-related pain crisis (SCPC) (also known as VOC leading to a healthcare visit) and delay of onset of VOC leading to a healthcare visit in a well-controlled Phase II clinical trial (SUSTAIN study) in a clearly defined SCD patient population. Treatment with crizanlizumab at 5.0 mg/kg was also found to be well tolerated [redacted] The substantial efficacy and acceptable safety of crizanlizumab suggest an overall favorable benefit-risk assessment and warrant further clinical development in SCD.

[redacted]

Crizanlizumab was well tolerated in SUSTAIN study. There were no unexpected safety findings; however, infusion-related reactions were observed in around 2% of subjects.

The risk of infections and serious infections with the use of crizanlizumab has been evaluated and the results suggest that the risk of infections and serious infections in crizanlizumab and placebo groups was similar.

Monoclonal antibodies (mAbs) are large molecules intended to bind to specific targets often expressed on the immune system, and to treat various immunopathological conditions. Therefore, mAbs can be considered to have a high potential for immunotoxicity, which is reflected in the clinical experience accumulated on mAbs-induced adverse effects related to immunosuppression, immunostimulation and hypersensitivity (immunogenicity) (Descotes J, 2009). So far, clinical studies have shown no deleterious effects of the use of crizanlizumab in regards to immunotoxicity and immunogenicity.

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 6.4. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as, close clinical monitoring, and in-patient status for 24 hours following the first dose. There may be unforeseen risks with crizanlizumab, which could be serious. For additional safety information, refer to the latest Investigator's Brochure.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
Characterize PK of crizanlizumab at 5.0 mg/kg in SCD patients	-PK parameters after the starting dose and after multiple doses. -Pre-dose concentrations prior to each study drug dose.	
Characterize PD (P-selectin inhibition) of crizanlizumab at 5.0 mg/kg in SCD patients	-%P-selectin inhibition and PD-AUC after the starting dose, after multiple doses, and prior to each study drug dose.	
Secondary		Refer to Section 10.5
Assess efficacy of crizanlizumab	-Annualized rate of VOC events leading to healthcare visit in clinic/ER/hospital -Annualized rate of VOC events treated at home (based on documentation by health care provider following phone contact with patient) -Annualized rate of hospitalizations and ER visits (both total and VOC-related) -Annualized days of ER/hospitalization (both total and VOC-related) -Annualized rate of each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism) -Annualized rate of VOC events (including both healthcare visit and home treatment)	
Assess safety and tolerability of crizanlizumab	-Number, seriousness, severity, and causality assessments of treatment emergent adverse events and other safety data as considered appropriate -Absolute change from baseline in hemoglobin -Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab	

[redacted]

4 Study design

4.1 Description of study design

This is a multicenter, single-arm, open-label study to assess PK and PD of crizanlizumab in adult patients with SCD and VOC.

Approximately 55 patients will be enrolled in the trial. 45 eligible patients (all screening criteria met) will be treated with crizanlizumab at a dose of 5.0 mg/kg and up to 10 additional eligible patients (all screening criteria met) will be treated with crizanlizumab at a dose of 7.5 mg/kg.

The study will include adult patients, ages 16-70 years, with confirmed diagnosis of SCD (genotypes HbSS, HbSC, HbS β^0-thalassemia, HbS β^+-thalassemia, and others) who have experienced at least 1 VOC within the preceding 12 months. Patients may not plan to initiate HU/HC during the study. For patients who are already treated with HU/HC, they should be taking HU/HC for at least 6 months and plan to continue the same dose at the same schedule during the trial

Patients will receive treatment until study treatment is permanently discontinued due to unacceptable toxicity, death, are lost to follow-up or discontinued from the study treatment for any other reasons. Patients will be followed in the mandatory safety follow-up period until 105 days after the last dosing. Patients continuing to receive benefit, defined as no evidence of increased frequency of VOCs and no severe adverse events attributed to drug as per Investigator's assessment, will remain on study until crizanlizumab is commercially available or until patients are rolled over in a different crizanlizumab study or access program.

Screening phase

Within 35 days before enrolment, the patient will provide a main signed informed consent form prior to any study related activities. All screening evaluations must be performed during the screening period (day-35 to day-1).

Treatment phase

Once eligibility criteria have been confirmed to Novartis via the eligibility checklist, the patient will be enrolled in the trial and will receive crizanlizumab. Study treatment should be started as soon as possible.

Patients may be admitted to the study site prior to dosing for baseline evaluations. The first 45 patients will receive crizanlizumab 5.0 mg/kg by IV infusion over 30 min on week 1 day 1, week 3 day 1, and then day 1 of every 4-week cycle. No dose change or modification will be allowed in the study for patients assigned to 5.0 mg/kg dose. Once 27 patients have evaluable PK/PD data (or a total of 45 patients are enrolled) at the 5.0 mg/kg dose, an exploratory cohort of 10 patients will be enrolled at a dose of 7.5 mg/kg. Patients will receive crizanlizumab 7.5 mg/kg by IV infusion over 30 min on week 1 day 1, week 3 day 1, and then day 1 of every 4-week cycle. Dose change or modifications are described in the Section 6.3.

All enrolled patients will have PK/PD sampling performed in order to characterize the PK/PD of crizanlizumab (see Table 7-5). On week 1 day 1 and week 15 day 1 the patients may be asked

[redacted]

to remain at the study site for at least 24 hours post dose in order to complete the PK/PD sample collection.

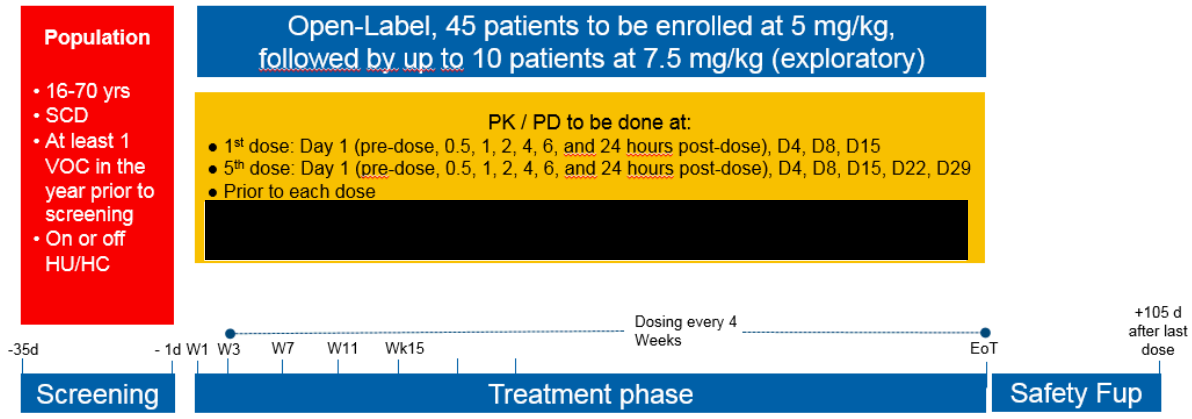
In case of VOC, the related medical and treatment information will be collected. [redacted]

Safety will be monitored as outlined in Section 8. Patients will receive treatment until unacceptable toxicity, death, are lost to follow-up or discontinued from the study treatment for any other reasons.

Post-treatment follow-up phase

After the end of treatment visit, all patients will be followed up for safety up to 105 days (15 weeks) after the last dose of study treatment.

Figure 4-1 Study Design



4.2 Timing of interim analyses and design adaptations

Exploration of early access (EA) PK data may occur for preliminary PK analysis prior to clinical data base lock. PK samples may be batched and shipped for expedited EA PK analysis and data will be uploaded by the bioanalyst via PKLink. For the derivation of PK parameters nominal time instead of actual elapsed time may be used.

An interim analysis may be performed when there are at least 27 patients with single dose evaluable PK profiles and approximately 5 patients with both single dose and multiple dose evaluable PK profiles in the 5.0 mg/kg treatment group in the Pharmacokinetic Analysis Set 1 (PAS1). This interim analysis may further characterize the PK/PD profile for the pediatric study CSEG101B2201; however there is currently no plan for design adaptation of trial CSEG101A2202. Another interim analysis may be performed when there are approximately 15 patients with multiple dose evaluable PK profiles in the 5.0 mg/kg treatment group in the PAS1, in order to inform the PK/PD/safety profile of crizanlizumab and potentially support the regulatory filing. Should the criteria for the two interim analyses be reached at similar times

[redacted]

compatible with both objectives, a single combined interim analysis will be performed. Additional earlier or later ad hoc interim analyses of PK/PD/safety may be performed in order to support potential Health Authority requests.

4.3 Definition of end of study

The primary analysis will be conducted after the PK and PD parameters are available for at least 27 patients in the 5.0 mg/kg treatment group in the Pharmacokinetic Analysis Set 1 (PAS1) and Pharmacodynamics Analysis Set 1 (PDS1) respectively. The primary analysis data will be summarized in the primary clinical study report (CSR).

Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. Ongoing patients will continue to receive study treatment and be followed as per the schedule of assessments, as long as patients derive benefit from crizanlizumab. The end of study is defined by the occurrence of one of the following:

- All patients have died or discontinued from the study
- Crizanlizumab is commercially available for this patient population, and patients obtain the commercial drug
- Another clinical study becomes available that can continue to provide crizanlizumab in this patient population and all patients ongoing are transferred to that clinical study

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

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient.

Premature study termination must occur if one or more of the following reasons apply:

- Decision of the Sponsor
- Safety issues: If more than 25% of the subjects at any time point have been withdrawn due to adverse events or abnormal laboratory results and abnormal test procedure results related to the study drugs.
- If information becomes available that the use of crizanlizumab would expose the subjects to an unacceptable risk.

In the event the safety stopping criteria are met, the Sponsor and Principal Investigator will discuss the implications of study continuation.

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

[redacted]

5 Population

5.1 Patient population

CSEG101A2202 will enroll up to 55 SCD patients (any genotype) ages 16-70 years who experienced at least 1 VOC over the preceding 12 months, and who are not planning to take HU/HC during the trial or who have been taking HU/HC for at least 6 months and plan to continue taking at the same dose and schedule during the trial.

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

5.2 Inclusion criteria

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

1. Male or female, 16 to 70 years of age (inclusive) on the day of informed consent signature.
2. Confirmed diagnosis of sickle cell disease by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) [performed locally]. All sickle cell disease genotypes are eligible (HbSS, HbSβ^0, HbSC, HbSβ^+, and others), though genotyping is not required for study entry.
3. Experienced at least 1 VOC within the preceding 12 months prior to Screening as determined by medical history. Prior VOC should include the occurrence of appropriate symptoms, a visit to a medical facility and/or healthcare professional, and receipt of parenteral opioid or NSAID analgesia or oral opioid.
4. If receiving HU/HC or erythropoietin stimulating agent, must have been receiving the drug for at least 6 months prior to Screening and plan to continue taking at the same dose and schedule during the trial.
5. Patient must meet the following laboratory values at the screening visit:
   - Absolute Neutrophil Count $\geq 1.0 \times 10^9$/L
   - Platelets $\geq 75 \times 10^9$/L
   - Hemoglobin (Hgb) ≥ 4.0 g/dL
   - Glomerular filtration rate $\geq$ 45 mL/min/1.73 m^2 using CKD-EPI formula
   - Direct (conjugated) bilirubin ≤ 2.0 x ULN
   - Alanine transaminase (ALT) $\leq$ 3.0 x ULN
6. ECOG performance status ≤ 2
7. Written informed consent, and applicable adolescent assent and parental consent for minor subjects, must be obtained prior to any screening procedures.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. History of stem cell transplant.
2. Acute vaso-occlusive crisis ending within 7 days prior to Week 1 Day 1 dosing.

[redacted]

3. Received blood products within 30 days of Week 1 Day 1 dosing.
4. Participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes).
5. Planning on undergoing an exchange transfusion during the duration of the study; episodic transfusion in response to worsened anemia or vaso-occlusive crisis is permitted.
6. Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation.
7. 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.
8. Use of therapeutic anticoagulation (prophylactic doses permitted) or antiplatelet therapy (other than aspirin or NSAIDs) within the 10 days prior to Week 1 Day 1 dosing
9. Received a monoclonal antibody or immunomodulatory agent within 1 year of Screening, or has documented immunogenicity to a prior biologic
10. Received active treatment on another investigational trial within 30 days (or 5 half-lives of that agent, whichever is greater) prior to Screening or plans to participate in another investigational drug trial
11. Pregnant or nursing women
12. 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 subject. 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). The vasectomized male partner should be the sole partner for that subject
    - 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.

13. Current drug or alcohol abuse:
    - Has a positive qualitative urine drug test at Screening for cocaine, phencyclidine (PCP), or amphetamines

[redacted]

- Consumes >12 (for males) or >8 (for females) standard alcoholic beverages per week

14. Any documented history of a clinical stroke or intracranial hemorrhage, or an uninvestigated neurologic finding within the past 12 months before Screening. Silent infarct only present on imaging is allowed.
15. Patients with bleeding disorders
16. Planning to undergo a major surgical procedure during the duration of the study
17. Hospitalized at Screening
18. Poorly-controlled HIV infection (CD4 count <200 cells/mm3 or viral load >50 copies/mL)
19. Patients with active Hepatitis B infection (HBsAg positive) will be excluded
    - Note: Patients with antecedent but no active Hepatitis B (i.e. anti-HBc positive , HBsAg and HBV-DNA negative) are eligible
20. Patients with positive test for hepatitis C ribonucleic acid (HCV RNA)
    - Note: Patients in whom HCV infection resolved spontaneously (positive HCV antibodies without detectable HCV-RNA) or those that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA ≥ 6 months (with the use of IFN-free regimes) or ≥ 12 months (with the use of IFN-based regimes) after cessation of antiviral treatment are eligible
21. Significant active infection or immune deficiency (including chronic use of immunosuppressive drugs)
22. Malignant disease. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma in situ
23. Has a serious mental or physical illness, which, in the opinion of the Investigator would compromise participation in the study
24. Any condition which, in the opinion of the investigator, is likely to interfere with the successful collection of the measurements required for the study.
25. Resting QTcF ≥470 msec at pretreatment (baseline)
26. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG), or uncontrolled congestive heart failure within 6 months prior to starting study treatment
    - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
      - Risk factors for Torsade de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia

[redacted]

- Concomitant medication(s) with a "Known risk of Torsade de Pointes" per wwwqtdrugsorg that cannot be discontinued or replaced by safe alternative *medication* (within 5 half-lives prior to starting study drug)
- Inability to determine the QTcF interval

27. Not able to understand and to comply with study instructions and requirements.

6 Treatment

6.1 Study treatment

Novartis will supply crizanlizumab (SEG101) as an open label medication. The investigational drug will be the crizanlizumab - SEG101 Histidine/Citrate buffered solution – provided every 4 weeks with an additional loading dose 2 weeks after the first dosing (i.e. dosing on first day of week1, week3, week7, and then every 4 weeks) until the end of study.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
SEG101	Intravenous infusion	5.0 mg/kg or 7.5 mg/kg	Week 1 Day 1, Week 3 Day 1, Week 7 Day 1 and day 1 of every 4-week cycle

Crizanlizumab is provided in single use vials containing 10 mL at a concentration of 10 mg/mL. The crizanlizumab formulation is a Histidine/Citrate buffered solution which is supplied in single use vials at a concentration of 10 mg/mL.

Each patient receives one dose of crizanlizumab on Week 1 Day 1, Week 3 Day 1, Week 7 Day 1 and day 1 of every 4-week cycle. On infusion day, the pharmacist or designated personnel will compound individual doses of crizanlizumab for patients on a milligram per kilogram basis in a 100 mL infusion bag of a sterile 0.9% sodium chloride solution (0.9% Sodium Chloride Injection, USP) in accordance with the Pharmacy Manual. Study drug will be administered over 30 minutes by IV infusion.

After the primary analysis, and considering that the drug product development is still ongoing to provide robust shelf-life, crizanlizumab Histidine/Citrate buffered solution may be substitute by the Final Market Image (FMI), citrate buffered solution. Minor modifications in the final buffer composition are expected and will be covered by in-vitro comparability studies.

6.1.2 Ancillary treatments

Not applicable.

[redacted]

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to Section 6.3 Dose modifications.

Patients who permanently discontinue the study drug 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

Patients will be treated until the earliest occurrence of one of the following (see Section 7.1.4):

- All patients have died or discontinued from the study
- Crizanlizumab is commercially available for this patient population, and patients are eligible to be prescribed the commercial drug
- Another clinical study becomes available that can continue to provide crizanlizumab in this patient population and all patients ongoing are eligible to be transferred to that clinical study

6.2 Dose escalation guidelines

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment until the next dose scheduled. **Dose reductions are only allowed for patients assigned to 7.5 mg/kg dose**. **No dose reductions are allowed in the study for patients assigned to 5.0 mg/kg dose who just have option for dose interruption.** The dose reduction is only in one level: from 7.5 mg/kg to 5.0 mg/kg and it is recommended at the grade 2 or 3 or higher for the CTCAE or otherwise mentioned in Table 6-2 and Table 6-3. If drug-induced toxicities are present, patients would have to be closely monitored and a decision to continue or discontinue the patient from the study would have to be done at the next dose scheduled.

These dose interruptions / reductions are summarized in Table 6-4. Deviations to mandatory dose interruptions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-4 or listed in Section 7.1.5.1.

Missing 2 consecutive doses (no dose for 10 weeks) would be considered criteria for permanently discontinuing the patient from the study.

Any dose changes must be recorded on the Dosage Administration Record CRF.

[redacted]

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

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Recommendation: maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Recommendation: maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	- Recommendation: interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists permanently discontinue the patient from the study. - *Recommendation for 7.5 mg/kg dosed patients only*: ↓ 1 dose level to 5 mg/kg. If after the reduction of dose the abnormality improves to ≤ Grade 2 re-escalation to 7.5 mg is allowed.
Grade 4 (ANC < 500/mm^3)	**Mandatory**: Interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists permanently discontinue the patient from the study.
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.3°C) A disorder characterized by an ANC <1000/mm^3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C	**Mandatory**: Interrupt dose until resolved or next dose schedule. If abnormality persists permanently discontinue the patient from the study.
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	May maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	May maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	- Recommendation: interrupt dose until resolved to ≤ Grade 1 or next dose scheduled. If abnormality persists permanently discontinue the patient from the study, then: - If resolved in ≤ 7 days, then maintain dose level

[redacted]

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	
	- If resolved in > 7 days, then ↓ 1 dose level (for 7.5 mg/kg dosed patients only: reduction to 5 mg/kg dose). If after the reduction of dose the abnormality improves to ≤ Grade 2 re-escalation to 7.5 mg is allowed.
Grade 4 (PLT < 25,000/mm^3)	**Mandatory**: Interrupt dose until resolved to ≤ Grade 1 or next dose scheduled. If abnormality persists permanently discontinue the patient from the study.
Investigations (Renal)	
Serum creatinine	
Grade 1 (>1.0 – 1.5 x baseline OR > ULN - 1.5 x ULN)	May maintain dose level
Grade 2 (> 1.5 – 3.0 x baseline OR > 1.5 - 3.0 x ULN)	- Recommendation: interrupt dose until resolved to ≤ Grade 1 or baseline level or next dose scheduled. If abnormality persists permanently discontinue the patient from the study. - *Recommendation for 7.5 mg/kg dosed patients only*: ↓ 1 dose level to 5 mg/kg. If after the reduction of dose the abnormality improves to ≤ Grade 1 re-escalation to 7.5 mg is allowed.
Grade 3 (> 3.0 x baseline OR > 3.0 - 6.0 x ULN)	- Recommendation: interrupt dose until resolved to ≤ Grade 1 or baseline level or next dose scheduled. If abnormality persists permanently discontinue patient from study drug treatment. - *Recommendation for 7.5 mg/kg dosed patients only*: ↓ 1 dose level to 5 mg/kg. If after the reduction of dose the abnormality improves to ≤ Grade 1 re-escalation to 7.5 mg is allowed.
Grade 4 (> 6.0 x ULN)	- **Mandatory**: interrupt dose until resolved to ≤ Grade 1 or baseline level or next dose scheduled. If abnormality persists permanently discontinue the patient from the study. - *Recommendation for 7.5 mg/kg dosed patients only*: ↓ 1 dose level to 5 mg/kg. If after the reduction of dose the abnormality improves to ≤ Grade 1 re-escalation to 7.5 mg is allowed.
Investigations (Hepatic)	
Isolated total Bilirubin elevation	
Grade 1 (> 1.5 x ULN)	Recommendation: maintain dose level

[redacted]

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	
Grade 2 (> 1.5 – 3.0 x ULN)	Recommendation: maintain dose level
Grade 3 (> 3.0 - 10.0 x ULN*)	- Recommendation: - Interrupt dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. - Monitor for hemolysis - If resolved, then continue with next dose scheduled - *Recommendation for 7.5 mg/kg dosed patients only*: ↓ 1 dose level to 5 mg/kg after confirmation of no hemolysis. If after the reduction of dose the abnormality improves to ≤ Grade 2 re-escalation to 7.5 mg is allowed.
Grade 4 (> 10.0 x ULN*)	- **Mandatory**: - Interrupt dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. - Monitor for hemolysis - If resolved, then continue with next dose scheduled - *Recommendation for 7.5 mg/kg dosed patients only*: ↓ 1 dose level to 5.0 mg/kg after confirmation of no hemolysis. If after the reduction of dose the abnormality improves to ≤ Grade 1 re-escalation to 7.5 mg is allowed. - If abnormality persists permanently discontinue patient from study drug treatment. - The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3.0 x ULN)	Recommendation: maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	

[redacted]

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	
- For patients with baseline value ≤ 3.0 x ULN	- Recommendation: maintain dose level. 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
- For patients with baseline value > 3.0 -5.0 x ULN	- Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN) - For patients with baseline value ≤ 3.0 x ULN	- Recommendation: interrupt dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Then If resolved, maintain dose level
- For patients with baseline value > 3.0 -5.0 x ULN	- Maintain dose level. 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 ≤ 5.0 x ULN
Grade 4 (> 20.0 x ULN)	- Recommendation: interrupt dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0-5.0 x ULN), if reoccurs at > 20 x ULN, permanently discontinue patient from study drug treatment. - *Recommendation for 7.5 mg/kg dosed patients only*: ↓ 1 dose level to 5.0 mg/kg. If after the reduction of dose the abnormality improves to ≤ Grade 2 re-escalation to 7.5 mg is allowed.
Combined [c] elevations of AST or ALT and bilirubin (direct [conjugated] and/or total)	
For patients with normal baseline ALT and AST and (direct or total) bilirubin value:	**Mandatory**: - Monitor for hemolysis.

[redacted]

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	
• AST or ALT >3.0xULN combined with direct or total bilirubin >2.0 x ULN without evidence of cholestasis OR (Note to study team: If supported by available data) For patients with elevated baseline AST or ALT or direct or total bilirubin value: • AST or ALT>2x baseline AND > 3.0 x ULN OR • AST or ALT > 8.0 x ULN, combined with [direct or total bilirubin >2x baseline AND >2.0 x ULN]	- If elevations of ALT and/or AST (>3.0 x ULN) and direct or total bilirubin (>2.0 x ULN) without evidence of cholestasis[d] (ALKP < 2 x ULN) are observed simultaneously at the [redacted] visit: interrupt dose and monitor for hemolysis. If abnormality persists without evidence of hemolysis, permanently discontinue patient from study drug treatment. Recommendation: If elevations of direct or total bilirubin precede the elevations of ALT and or AST, monitor for hemolysis. Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.3.1.1 for additional follow-up evaluations as applicable.
Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	May maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	May maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN)	Recommendation: interrupt dose until resolved to Grade ≤1 or baseline then: - If resolved, then maintain dose level - If resolved in > 7 days, then ↓ 1 dose level (for 7.5 mg/kg dosed patients only: reduction to 5 mg/kg dose). If after the reduction of dose the abnormality improves to ≤ Grade 2 re-escalation to 7.5 mg is allowed.
Grade 4 (> 5.0 x ULN)	**Mandatory**: interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists permanently discontinue the patient from the study.

[redacted]

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	
Gastro intestinal	
Pancreatitis	
Grade 2 (Enzyme elevation or radiologic findings only)	Recommendation : maintain dose level
Grade ≥ 3 - Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	**Mandatory**: interrupt dose and permanently discontinue patient from study drug treatment
Diarrhea* **	
Grade 1 (Increase of <4 stools per day over baseline)	May maintain dose level but, initiate anti-diarrhea treatment
Grade 2 (Increase of 4 - 6 stools per day over baseline)	Recommendation: - Interrupt dose until resolved to ≤ grade 1, then maintain dose level. - If diarrhea returns as ≥ grade 2, then interrupt dose until resolved to ≤ grade 1.
Grade 3 (Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated)	Recommendation: interrupt dose and permanently discontinue patient from study drug treatment
Grade 4 (Life-threatening consequences; urgent intervention indicated)	**Mandatory**: interrupt dose and permanently discontinue patient from study drug treatment
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1 - Macules/papules covering <10% Body Surface Area (BSA) with or without symptoms (e.g., pruritus, burning, tightness)	May maintain dose level. Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
Grade 2 - Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness)	May maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)

[redacted]

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	
Grade 3, despite skin toxicity therapy - Macules/papules covering >30% BSA with or without associated symptoms	Recommendation: - Interrupt dose until resolved to Grade ≤ 1, then: - If not resolved (despite appropriate skin toxicity therapy), then permanently discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	**Mandatory**: interrupt dose and permanently discontinue patient from study drug treatment
Fatigue (General disorders and administration site conditions). A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.	
Grade 1 (Fatigue relieved by rest)	May maintain dose level
Grade 2 (Fatigue not relieved by rest)	May maintain dose level
Grade 3 (Fatigue not relieved by rest, limiting self-care Activities of Daily Living)	Recommendation: - Interrupt dose until resolved to ≤ grade 1, then : - If resolved, then maintain dose level

[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03)

[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)

[c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction. Dose reductions are only allowed for patients assigned to 7.5 mg/kg dose. No dose reductions are allowed in the study for patients assigned to 5.0 mg/kg dose.

[d] "Cholestasis" defined as ALP elevation (>2.0 x ULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis

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

[redacted]

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (value) during a cycle of therapy	
* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), continue treatment at the discretion of the investigator. ** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment. *** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea	

[redacted]

Table 6-3 Management for drug-related toxicities

Toxicity	Management
Infusion-related reactions	
Grade 1	Decrease infusion rate until recovery
Grade 2	Stop infusion Before restarting - administer oral premedication (e.g.1000 mg of acetaminophen/paracetamol, 50-100 mg diphenhydramine hydrochloride or alternative antihistamine), within 60 minutes of restarting the infusion. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s). If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then discontinue patient from study.
Grade 3 and 4	Discontinue study treatment

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

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Monitoring for hemolysis in subjects with elevations of TBIL > 2.0 x ULN should be performed to rule out a plausible explanation of increase of TBIL.

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

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

[redacted]

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, 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, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug.
5. Additional 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.
6. If elevations of total bilirubin precede the elevations of ALT and or AST, monitoring for hemolysis.

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", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.1.2 Dose adjustments for QTcF prolongation

In case of QTcF >500 msec, (or QTcF prolongation >60 msec from baseline)

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes" and drugs with the potential to increase the risk of study drug exposure related QT prolongation (See Appendix 2)
5. Check study drug dosing schedule and treatment compliance
6. Consider collecting a time-matched PK sample and record time and date of last study drug intake.

After confirming ECG reading at site, if QTcF > 500 msec (or QTcF prolongation >60 msec from baseline)

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec.

[redacted]

- After resolution to ≤ 480 msec, consider re-introducing treatment at reduced dose (for 7.5 mg/kg only), and increase ECG monitoring for the next treatment(s):
  - If QTcF remains ≤ 500 msec after dose reduction, continue planned ECG monitoring during subsequent treatment
  - If QTcF recurs > 500 msec after dose reduction, discontinue patient from trial.

6.4 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted (see Section 6.4.1), except as specifically prohibited (see Section 6.4.2).

The patient 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, Surgical and Medical Procedures or Transfusion page of the CRF.

6.4.1 Permitted concomitant therapy

Concomitant sickle cell therapy with hydroxyurea or hydroxycarbamide is permitted, provided the patient has been prescribed HU/HC consistently over at least the 6 months prior to enrollment, as stated in the Inclusion criteria. Erythropoietin-stimulating agents are also permitted to manage chronic symptomatic anemia with the same requirement for 6 months prior therapy as HU/HC. L-glutamine oral powder (Endari) is also permitted without restriction. Aspirin, NSAIDs and prophylactic doses of anticoagulants are permitted, while other anti-platelets agents or anticoagulants at doses targeting therapeutic levels are prohibited.

All FDA-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.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Although transfusion of cellular blood products is permitted, it is unclear how such transfusions will impact the PK and/or PD of crizanlizumab, [redacted] It should also be considered that the administration of products containing immunoglobulins (plasma, IVIG, anti-globulins) may also impact the efficacy of crizanlizumab, and optional PK and PD testing may also be performed prior to and following administration of such therapies.

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 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, [redacted]

vitamin E, and Zinc) are also permitted, though caution is advised when taking amounts exceeding 100% of the recommended daily allowance.

6.4.3 Prohibited concomitant therapy

As far as possible avoid co-administering drugs with a "Known", "Possible", or "Conditional" risk of Torsades de Pointes (TdP) as per wwwqtdrugsorg during the course of the study:

- If concomitant administration of drugs with a "Known risk of Torsades de Pointes" is required and cannot be avoided, study drug must be interrupted. Study treatment may only be resumed after 5 half-lives (of the QT-prolonging drug) from last dose of the QT prolonging drug, and close ECG monitoring is advised.
- If during the course of the study, concomitant administration of a drug with ¨Possible risk¨ or ¨Conditional risk of Torsades de Pointes¨ is required, based on the investigator assessment and clinical need, study treatment may be continued under close ECG monitoring to ensure patient safety.

A list of drugs associated with QT prolongation and/or TdP is available online at wwwqtdrugsorg.

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

Infusion-type reactions were rarely reported in prior studies with crizanlizumab, so prophylaxis for such reactions is not recommended. If a patient experiences severe infusion-related reaction, study drug should be discontinued and appropriate treatment provided.

6.4.4 Use of Bisphosphonates (or other concomitant agents)

Not applicable

6.5 Subject numbering, treatment assignment or enrolment

6.5.1 Subject numbering

Each patient is identified in the study by a Subject Number (Subject No.) (7 digits), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No. 4 digits) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it (3 digits), so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Clinical Data Management System interface.

[redacted]

6.5.2 Treatment assignment or Enrolment

The first 45 patients will be assigned to the 5.0 mg/kg crizanlizumab treatment, while the 10 next enrolled patients will be assigned to the 7.5 mg/kg crizanlizumab treatment (Section 4.1 and Section 6.1). The assignment of a patient to a particular treatment dose will be confirmed by the sponsor based on the actual enrolment.

6.5.3 Treatment blinding

This is an open label study. Investigators, patients and Sponsor will have full knowledge of the treatment allocation. In order to minimize the potential impact of the treatment knowledge, until the primary analysis is conducted, no aggregated statistical analyses (efficacy or safety across the study) shall be performed by treatment (other than analyses as specified in the study protocol).

6.6 Study drug preparation and dispensation

Crizanlizumab will be prepared by a pharmacist or study personnel appropriately trained in the preparation of liquids for parenteral administration (use aseptic techniques when preparing the study drug solution). Only compatible material tested during compatibility should be used for the administration of crizanlizumab.

Prior to administration, the crizanlizumab admixture should be allowed to warm to room temperature by exposure to ambient air. Do not heat thecrizanlizumab admixture in a microwave or with any heat source other than ambient air temperature. The crizanlizumab study drug product should only be administered via IV infusion including a 0.2µm inline filter and must be diluted prior to administration.

NOTE: **DO NOT ADMINISTER THE STUDY DRUG AS AN IV PUSH OR BOLUS INJECTION.** After administration of study drug (5.0 mg/kg crizanlizumab or 7.5 mg/kg crizanlizumab), a 25 mL flush of the IV line will occur. Site personnel should ensure availability of at least 25 mL of sterile 0.9% sodium chloride solution (0.9% Sodium Chloride Injection, USP) for administration after that of study drug.

Prepared infusion solution in infusion bag should be used immediately, and must be within 4 hours of preparation.

If the selected center for the clinical study is located in US and is USP<797> compliant, the preparation and handling of the infusion bags shall comply with the guidance given in the USP but is limited to the physico-chemical stability demonstrated as indicated below.

If the selected center for the clinical study is located in US and is NOT USP<797> compliant, from a microbiologic point of view, the ready mixed infusion bag shall be used immediately and not be held for longer than four hours at room temperature from the moment the first vial is pierced till the start of administration.

The compounded 0.9% sodium chloride (saline) bag with crizanlizumab should be intravenously administered over 30 minutes. It is not necessary to protect the infusion bags from light (still direct sun light should be avoided) while study drug is being administered to the patient. At the site's discretion, the crizanlizumab saline bag may be administered via gravity feed, a syringe-type pump, or an infusion pump. Following completion of the study drug

[redacted]

infusion, at least another 25 mL 0.9% sodium chloride should be administered in order to clear the infusion line of drug and ensure all study drug has been administered to the patient. The patient should be monitored for one (1) hour following infusion. For more details please refer to the [Pharmacist Manual].

6.6.1 Study treatment packaging and labeling

Study treatment, crizanlizumab, will be provided as global clinical open supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength) or randomization number if appropriate.

Table 6-4 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
SEG101	Vials containing 10 mL at a concentration of 10 mg/mL	Labeled as 'SEG101' (at Week1 Day1, Week3 Day 1, Week 7 Day 1 and at Day 1 of every 4-weeks)

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly (protected from light, refer to the pharmacy manual and labels for more detail), and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified in the [Pharmacy Manual] and in the [Investigator's Brochure].

Table 6-5 Supply and storage of study treatments

Study treatments	Supply	Storage
SEG101	Centrally supplied by Novartis	Refer to study treatment label

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and 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.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

Allowed visit windows are specified as follows:

- Screening assessments, apart from those listed below, must occur within 35 days prior to the enrolment as per Table 7-1.
- No visit window is allowed Week 1 Day 1 to Week 2 Day 1. And from Week 15 Day 1 to Week 16 Day 1 (or following the first week of steady state as specified in Table 7-5).
- A ±1 days visit window is permitted on assessments Week 3 Day 1, Week 17 Day 1 and Week 18 Day 1
- For all other visits a general ±3 days visit window is permitted on assessments to take into account scheduling over public holidays.
- A + 7 days for the end of post-treatment phase (last infusion + 105 days) is allowed

Every effort should be made to follow the schedule outlined in Table 7-1.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening phase	Treatment phase														End of treatment (EoT)	Follow up phase
Visit on Day1 of the week (unless otherwise specified)[a]			**D-35 to D-1**	**Wk1**	**Wk1 D2**	**Wk1 D4**	**Wk2**	**Wk3**	**Wk7**	**WK11**	**Wk15**	**Wk15 D2**	**Wk15 D4**	**Wk16**	**Wk17**	**Wk18**	**Wk 19, 23, 27, 31, 4qWk**	**Within 7 days of last infusion**	**Last infusion + 105d**
Screening																			
Obtain Study Informed Consent	D	7.1.2	X																
[redacted]																			
Disposition assessment																			
Study disposition	D	7	X															X	X
Patient history																			
Demography	D	7.1.2.3	X																
Inclusion/exclusion criteria	D	7.1.2.1	X																
Medical History	D	7.1.2.3	X																
ECOG performance status	D	7.2.2.4	X																
Sickle Cell – Vaso-Occlusive Crisis history	D	7.1.2.3	X																
Alcohol history	D	7.1.2.3	X																

[redacted]

	Category	Protocol Section	Screening phase	Treatment phase														End of treatment (EoT)	Follow up phase
Visit on Day1 of the week (unless otherwise specified)[a]			**D-35 to D-1**	**Wk1**	**Wk1 D2**	**Wk1 D4**	**Wk2**	**Wk3**	**Wk7**	**WK11**	**Wk15**	**Wk15 D2**	**Wk15 D4**	**Wk16**	**Wk17**	**Wk18**	**Wk 19, 23, 27, 31, 4qWk**	**Within 7 days of last infusion**	**Last infusion + 105d**
Smoking history	D	7.1.2.3	X																
Drug Screen (drug, alcohol)[d]	S / D	7.2.2.5	X																
Physical examination																			
Physical examination	S	7.2.2.1	X															X	
Abbreviated physical exam	S	7.2.2.1		X				X	X	X	X						X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	D	7.2.2.3	X																
Weight	D	7.2.2.3	X	X				X	X	X	X						X		
Laboratory assessments		7.2.2.5																	
Hematology	D	7.2.2.5.1	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.5.2	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	D	7.2.2.5.4	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (microscopic or macroscopic)	D	7.2.2.5.3	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

	Category	Protocol Section	Screening phase	Treatment phase														End of treatment (EoT)	Follow up phase
Visit on Day1 of the week (unless otherwise specified)[a]			**D-35 to D-1**	**Wk1**	**Wk1 D2**	**Wk1 D4**	**Wk2**	**Wk3**	**Wk7**	**WK11**	**Wk15**	**Wk15 D2**	**Wk15 D4**	**Wk16**	**Wk17**	**Wk18**	**Wk 19, 23, 27, 31, 4qWk**	**Within 7 days of last infusion**	**Last infusion + 105d**
Serum pregnancy test	S	7.2.2.5.5	X															X	X
Urine pregnancy test	S	7.2.2.5.5		X				X	X	X	X						X		
Hepatitis testing	D	7.2.2.5.6	X																
HIV test	D	7.2.2.5.7	X																
Efficacy assessments		7.2.1																	
Sickle Cell – Vaso-Occlusive Crisis Event	D	7.2.1		Continuous															
Chest x-ray	D	7.2.1	X[e]																
Hospitalization	D	7.2.1		Continuous															
Prior/concomitant medications – Analgesic	D	6.4	X	Continuous															
Prior/concomitant medications – Hydroxyurea	D	6.4	X	Continuous															
Transfusion	D	7.2.1	X	Continuous															
Employment status and sick time	D	7.2.1	X	X				X	X	X	X						X	X	
Safety assessments																			
ECG	D	7.2.2.6.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X	X

[redacted]

	Category	Protocol Section	Screening phase	Treatment phase													End of treatment (EoT)	Follow up phase
Visit on Day1 of the week (unless otherwise specified)[a]			**D-35 to D-1**	**Wk1**	**Wk1 D2**	**Wk1 D4**	**Wk2**	**Wk3**	**Wk7**	**WK11**	**Wk15**	**Wk15 D2**	**Wk15 D4**	**Wk16**	**Wk17**	**Wk18**	**Wk 19, 23, 27, 31, 4qWk**	**Within 7 days of last infusion**	**Last infusion + 105d**
[redacted]																		
[redacted]																		
Adverse Event/ Serious Adverse Event	D	8	X	Continuous														
Prior/concomitant medications	D	6.4	X	Continuous														
[redacted]																		

[redacted]

	Category	Protocol Section	Screening phase	Treatment phase														End of treatment (EoT)	Follow up phase
Visit on Day1 of the week (unless otherwise specified)[a]			**D-35 to D-1**	**Wk1**	**Wk1 D2**	**Wk1 D4**	**Wk2**	**Wk3**	**Wk7**	**WK11**	**Wk15**	**Wk15 D2**	**Wk15 D4**	**Wk16**	**Wk17**	**Wk18**	**Wk 19, 23, 27, 31, 4qWk**	**Within 7 days of last infusion**	**Last infusion + 105d**
[redacted]																			
Pharmacokinetics																			
PK sampling[g]	D	7.2.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]		X
Immunogenicity																			
Immunogenicity sampling	D	7.2.3		X				X	X	X	X						X[c]		X
Study Drug administration																			
Crizanlizumab IV	D	6.1.1		X				X	X	X	X						X		

[a] In case the study drug is interrupted, the dose should be resumed as soon as possible. If the dose is delayed for more than 7 days, all future visits should be rescheduled from the date of the last infusion.

[b] Assessments to be done at within 14 days of Week 1 Day 1 dosing, if the screening assessments have been done more than 14 days before Week 1 Day 1.[c] From week 51 will be done every 24 weeks (Wk 75, 99, 123, 147 and 171 (See Table 7-4 and Table 7-5))

[d] Drug results will be captured in database. Blood alcohol screen result will be captured in source

[redacted]

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 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 7-1 for list of assessments to be performed). The investigator will obtain consent / assent of patients and/or parents according to local procedures.

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

In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria. A new informed consent form must be signed only if there is an interruption in the patient's eligibility evaluation and the investigator chooses to re-screen the patient following screen failure. If a new informed consent form is signed, AEs and medical history will be assessed relative to the new informed consent date.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range before screen failing the patient. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. For details of assessments, see Table 7-1.

[redacted]

7.1.2.1 Eligibility screening

The investigator is responsible to ensure only subjects who meet all inclusion and do not meet any exclusion criteria are included in the study.

Patient eligibility will be checked by the Sponsor once all screening procedures are completed. The eligibility check form will be sent from the site to the Sponsor via email for evaluation. Upon confirmation of eligibility, the Sponsor will assign the patient either to the 5.0 mg/kg or 7.5 mg/kg treatment group (according to the enrolment chronological order) and will return the signed eligibility check form via email to the site. The investigator site will then be allowed to assign treatment to the patient. Please refer and comply with detailed guidelines in the Eligibility check user guidelines.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be enrolled (patient who does not enter in the treatment phase) for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, Inclusion/Exclusion pages and, if applicable, withdrawal of informed consent must also be completed for Screen Failure patients. No other data will be

[redacted]

entered into the clinical database for patients who are screen failures, unless the patient experienced an SAE during the Screening Phase (see Section 8 for SAE reporting details).

If a screen failure patient experiences an AE which does not meet the SAE criteria, details about the AE will be recorded only in the investigator's source documents. In case of an SAE after signing of main study informed consent, data must be recorded on both the AE and SAE forms.

If the patient fails to be enrolled, the Sponsor must be notified within 2 days of the screen fail via email that the patient was not enrolled.

7.1.2.3 Patient demographics and other baseline characteristics

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

Background medical information, including Sickle Cell and Vaso –Occlusive Crisis History, ECG, relevant and current medical history and alcohol and smoking history will also be collected.

Other baseline characteristics and assessments performed at screening for eligibility are detailed in Table 7-1.

7.1.3 Run-in period

Not Applicable

7.1.4 Treatment period

The first 45 patients will receive crizanlizumab at 5mg/kg on week 1 day 1, week 3 day 1 and then every 4 weeks (week 7 day 1, week 11 day 1, etc.). Once 27 patients have evaluable PK and PD data (or a total of up to 45 patients are enrolled) at the 5.0 mg/kg dose, 10 additional patients will receive crizanlizumab at 7.5 mg/kg on week 1 day 1, week 3 day 1 and then every 4 weeks.

All patients will continue to receive study treatment and be followed as per the schedule of assessments, as long as patients derive benefit from crizanlizumab until any combination of the following will apply to all patients:

- All patients have died or discontinued from the study
- Crizanlizumab is commercially available for this patient population, and patients are eligible to be prescribed the commercial drug
- Another clinical study becomes available that can continue to provide crizanlizumab in this patient population and all patients ongoing are eligible to be transferred to that clinical study.

Full PK and PD profiles will be collected on week 1 days 1, 2 and 4, on day 1 of weeks 2, 3, 7 and 11. **From week 15 day 1, additional full PK and PD profiles will be collected on days 1, 2, and 4 of week 15 (or at the time of the fifth infusion), on day 1 of weeks 16, 17, 18 and 19.**

However, if the dose was interrupted and/or an infusion was delayed before week 15, then after 3 consecutive infusions have been given without an interruption of >7 days, the

[redacted]

additional full PK and PD profiles will be collected on days 1, 2, 4 of the week of the third consecutive infusion, and day 1 of the 4 consecutive weeks following the third infusion).

Pre-dose PK and PD sampling will be collected prior to each infusion until week 51. [redacted]

For details of assessments, see Table 7-1 and Table 7-5.

7.1.5 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

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

In addition to the mandatory reasons for discontinuation of study treatment listed in Section 6.3, study treatment **must** also be discontinued under the following circumstances:

- Pregnancy
- Lactation
- Death
- Subject/Guardian decision
- Adjustments to study treatment due to toxicity that result in treatment discontinuation (see Section 6.3)
- Use of prohibited medication (see Section 6.4).
- Any other protocol deviation that results in a significant risk to the patient's safety.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1 for an EOT visit and a safety Follow-Up visit. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.6.

Patients who discontinue study treatment should undergo an End of Treatment (EOT) visit followed by a 105 day safety follow-up. At EOT visit, all the assessments as listed in Table 7-1 will be performed. If the decision to discontinue the patient occurs at a regularly scheduled visit, that visit may serve as the EOT visit rather than having the patient return for an additional visit.

7.1.5.1 Replacement policy

Not Applicable

[redacted]

7.1.6 Withdrawal of consent

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

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

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

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 subject are not allowed unless safety findings require communicating or follow-up.

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

Novartis/sponsor will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations for 5 half-lives (105 days) after the last dose of study treatment. Once an AE is detected, investigators are required to follow this AE until its resolution or stabilization. Refer to Section 8.1.1 for definitions and reporting of AEs. Patients whose treatment is interrupted or discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first. This could include all study assessments appropriate to monitor the event.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

Any SAEs experienced after the 105 day safety evaluation follow-up period should be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting

[redacted]

the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

VOC is defined as pain crises (defined as an acute onset of pain for which in the opinion of the investigator there is no other medically determined explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids or parenteral NSAIDs) as well as other complicated crises, such as acute chest syndrome (ACS), priapism, and hepatic or splenic sequestration.

For purposes of this study, the following detailed definitions will be used to identify each sub-type of VOC event:

1. Uncomplicated pain crisis is defined as an acute episode of pain with no known cause for pain other than a vaso-occlusive event; and requiring treatment with a parenteral or oral opioids or parenteral NSAIDs; but is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration or priapism. The end of an uncomplicated pain crisis will be considered the resolution of acute pain, such that residual pain (or absence of any pain) is considered to be chronic, and the current pain medication regimen is considered to be for this chronic pain.
2. Acute Chest Syndrome (ACS) is defined on the basis of the finding of a new pulmonary infiltrate involving at least one complete lung segment that was consistent with alveolar consolidation, but excluding atelectasis (as indicated by chest X-ray). At least one of the following additional signs or symptoms needs to be present as well: chest pain, a temperature of more than 38.5°C, tachypnea, wheezing or cough. ACS will be considered resolved when the patient is no longer hospitalized (unless for reason other than the ACS episode) and none of the additional signs or symptoms above are present.
3. Priapism is defined as an unwanted or painful penile erection lasting at least 30 minutes. The end of an acute priapism event will be when the unwanted erection has resolved for at least 2 hours.
4. Hepatic sequestration is defined on the basis of findings of right upper quadrant pain, an enlarged liver, and an acute decrease in hemoglobin concentration (e.g. a decrease in hemoglobin of ~ 2 g/dL). Acute hepatic sequestration will be considered resolved when right upper quadrant pain has returned to baseline (pre-event) levels and hemoglobin has been stable for 24 hrs.
5. Splenic sequestration if defined on the basis of findings of left upper quadrant pain, an enlarged spleen, and an acute decrease in hemoglobin concentration (e.g., a decrease in hemoglobin of ~ 2 g/dL). Acute splenic sequestration will be considered resolved when left upper quadrant pain has returned to baseline (pre-event) levels and hemoglobin has been stable for 24 hrs.

[redacted]

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 VOC event. Similarly, complications such as pulmonary, cardiac, or renal failure are not themselves to be considered crises. If such events precipitate VOC, the VOC 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, patient treatment and management, course, duration of the crisis, and outcome. For patients who are treated at medical facilities other than the study site, summary documents (e.g. ER or hospital discharge summaries) will need to be obtained. Patients will be issued an investigational study participation card that requests this information and can be presented at each medical facility visit.

Patients should be encouraged to contact the Investigator (or surrogate from the site) when they believe they are experiencing a VOC that they believe they can manage at home, both for treatment guidance and for accurate information may be obtained for the VOC eCRF page. VOCs treated at home but not documented by a telephone call within 24 hours of onset will not be counted as a VOC, due to concern over the accuracy of patient recall of all relevant details.

If a patient experiences a VOC surrounding a protocol-scheduled visit day, and the patient 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). VOC is not a known contra-indication, but dosing during a crisis should be at investigator's discretion.

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

Chest X-Ray must be conducted within the 3 months prior to week 1 day 1 . Chest X-Ray must be repeated in case of suspected ACS.

Transfusion data should be collected from 30 days prior to Screening until the patient EOT visit. Patients participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) are not eligible. Episodic transfusion in response to worsened anemia or VOC is permitted.

Table 7-2 Vaso-Occlusion Crisis Assessment Collection Plan

Procedure / Assessment collection plan	Screening/Baseline	During Treatment/Follow-up
Chest X-Ray	Mandated	If clinically indicated
Vaso-Occlusion Crisis information	Mandated	Mandated, when VOC crisis occurs
Concomitant medication – Analgesic	If clinically indicated	Mandated, when VOC crisis occurs
Hospitalization details	If clinically indicated	Mandated, when VOC crisis occurs and hospitalization is done
[redacted]		

Procedure / Assessment collection plan	Screening/Baseline	During Treatment/Follow-up
Employment status and sick time	If clinically indicated	If clinically indicated
[redacted]		

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examinations, vital signs, ECG, laboratory assessments including hematology, chemistry, coagulation, urinalysis and as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

The physical examination must be performed by the Investigator as scheduled in Table 7-1.

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination will be performed at Screening and within 7 days following last infusion.

An abbreviated (short) physical exam will include the examination of general appearance and vital signs (blood pressure [BP] and pulse), as well as additional components of the physical exam, as needed based on observed signs or reported symptoms. A short physical exam will be performed at all visits for which there is a scheduled study drug infusion.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, respiratory rate and body temperature will be measured as specified in Table 7-1.

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at all visits for which there is a scheduled study drug infusion (for dosing), as specified in Table 7-1.

7.2.2.4 Performance status

ECOG performance status scale will be assessed at screening.

[redacted]

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses (hematology, chemistry, urinalysis, coagulation, hepatitis and HIV markers and drug screen) are to be performed centrally unless otherwise noted in Table 7-3 according to the schedule of assessments and collection plan outlined in Table 7-1. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Central Laboratory Manual/Flowchart. Visit windows are allowed for all visits (except from Week 1 Day to Week 2 Day 1 and Week 15 Day 1 to Week 16 Day 1 (or following the first week of steady state) see Section 7.1).

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

For assessment of patients' eligibility for the study, only laboratory results from the central laboratory will be used (except in case of re-sampling at Day -14 and the results from the central laboratory are not yet available or are partial at time of the first infusion, then eligibility may be based on the results from the local laboratory. In such case, the results of the local laboratory will need to be recorded in the eCRF unscheduled pages and copy of the local lab normal ranges must be provided).

Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) AE, if central laboratory results are unevaluable or inconclusive, 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

Common Terminology Criteria for Adverse events (CTCAE) version 4.03. Additional analyses are left to the discretion of the investigator.

Table 7-3 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Central: Hematocrit, Hemoglobin, MCH, MCHC, MCV, Hemoglobin electrophoresis or HPLC, 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	Central: Albumin, Alkaline phosphatase, ALT, AST, Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), Creatinine Clearance (eGFR), Local: Blood alcohol screen
Urinalysis	Local: Macroscopic Panel (Dipstick) will be done locally (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Central: Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) performed, if a positive dipstick. Central: Urine Drug Screen (Amphetamine, Barbiturate, Benzodiazepine, Cannabinoids, Cocaine, Methadone, Phencyclidine, Opiate, Tricyclics, Methamphetamine) [redacted]
Coagulation	Central: Prothrombin time (PT), International normalized ratio [INR], Partial thromboplastin time (PTT) or Activated partial thromboplastin time (APTT)
Hepatitis markers	Central: HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR, HCV Ab (at Screening only)
Additional tests	Central: HIV Ab (at Screening only)
Pregnancy Test	Central: Serum pregnancy test (at Screening, EoT and end of safety follow-up only), Local: urine pregnancy test (before each infusion).

7.2.2.5.1 Hematology

Hematology tests are to be performed centrally according to the schedule of assessments and collection plan outlined in Table 7-1. Detailed hematology panel is described on Table 7-3.

7.2.2.5.2 Chemistry

Chemistry tests are to be performed centrally (except blood alcohol screen test) according to the schedule of assessments and collection plan outlined in Table 7-1. Detailed chemistry panel is described on Table 7-3.

[redacted]

Glomerular filtration rate (using CKD-EPI formula) will be done centrally:

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

$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

Scr = serum creatinine (mg/dL)

7.2.2.5.3 Urinalysis

Macroscopic urinalysis dipstick analysis (WBC, blood, protein and glucose) will be performed locally according to the schedule of assessments and collection plan outlined in Table 7-1. Detailed urinalysis panel is described on Table 7-3.

Microscopic analysis will be performed centrally only in case of positive dipstick.

[redacted]

7.2.2.5.5 Pregnancy and assessments of fertility

All female subjects of childbearing potential must perform a central serum hCG pregnancy test at screening in order to confirm study eligibility, at End of Treatment and at the end of the post treatment follow-up 105 days after the last infusion.

At Week 1 Day 1 prior to receive the dose of crizanlizumab, and before all visits for which there is a scheduled study drug infusion, a locally performed urine pregnancy test will be performed.

Additional pregnancy test can be performed as soon as indicated in case the subject is suspected to be pregnant (urine or serum).

Each pregnancy in a subject on study drug must be reported to the sponsor within 24 hours of learning of its occurrence. See Section 8.4 for detailed reporting and follow up procedures.

7.2.2.5.6 Hepatitis markers

Hepatitis testing will be performed centrally as per Table 7-1.

[redacted]

7.2.2.5.7 Additional test

HIV and Drug screen will be performed centrally as per Table 7-1.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed (in the supine position) after the patient has been resting for 5-10 min prior to each time point indicated in Table 7-4. ECG assessments are to be done prior to blood collection sampling.

When triplicate ECG are required, the individual ECGs should be recorded approximately 2 minutes apart.

The QTcF values using Fridericia's correction (formula is provided below) should be used.

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

The mean QTcF value will be calculated from the triplicate ECGs for each patient. Unscheduled triplicate ECGs will be performed also in case QTcF ≥500 ms has been observed.

Table 7-4 Central ECG collection plan

Period	Week / Day	Time [a]	ECG Type
Screening	Day -28 to Day -1	Anytime	Triplicate 12 Lead
Treatment	Week 1 Day 1	Pre-dose	Triplicate 12 Lead
		0.5h post-dose (± 5 min end of infusion)	Triplicate 12 Lead
		1h post-dose (± 5 min)	Triplicate 12 Lead
		2h post-dose (± 30 min)	Triplicate 12 Lead
		4h post-dose (± 30 min)	Triplicate 12 Lead
		6h post-dose (± 30 min)	Triplicate 12 Lead
	Week 1 Day 2	24h post-dose (± 2 hr)	Triplicate 12 Lead
	Week 1 Day 4	72h post-dose (± 2 hr)	Triplicate 12 Lead
	Week 2 Day 1	7d post-dose (± 24 hr)	Triplicate 12 Lead
	Week 3 Day 1	Pre-dose [b]	Triplicate 12 Lead
	Week 7 Day 1	Pre-dose [b]	Triplicate 12 Lead
	Week 11 Day 1	Pre-dose [b]	Triplicate 12 Lead
	Week 15 Day 1	Pre-dose [b]	Triplicate 12 Lead
		0.5h post-dose (± 5 min end of infusion)	Triplicate 12 Lead
		1h post-dose (± 5 min)	Triplicate 12 Lead
		2h post-dose (± 30 min)	Triplicate 12 Lead
		4h post-dose (± 30 min)	Triplicate 12 Lead
		6h post-dose (± 30 min)	Triplicate 12 Lead
	Week 15 Day 2	24h post-dose (± 2 hr)	Triplicate 12 Lead
	Week 15 Day 4	72h post-dose (± 2 hr)	Triplicate 12 Lead

[redacted]

Period	Week / Day	Time [a]	ECG Type
	Week 16 Day 1	7d post-dose (± 24 hr)	Triplicate 12 Lead
	Week 17 Day 1	14d post-dose (± 24 hr)	Triplicate 12 Lead
	Week 18 Day 1	21d post-dose (± 24 hr)	Triplicate 12 Lead
	Week 19 Day 1	Pre-dose [b]	Triplicate 12 Lead
	Week 23 Day 1	Pre-dose [b]	12 Lead
	Week 27 Day 1	Pre-dose [b]	12 Lead
	Week 31 Day 1	Pre-dose [b]	12 Lead
	Week 35 Day 1	Pre-dose [b]	12 Lead
	Week 39 Day 1	Pre-dose [b]	12 Lead
	Week 43 Day 1	Pre-dose [b]	12 Lead
	Week 47 Day 1	Pre-dose [b]	12 Lead
	Week 51 Day 1	Pre-dose [b]	12 Lead
	Week 75 Day 1	Pre-dose [b]	12 Lead
	Week 99 Day 1	Pre-dose [b]	12 Lead
	Week 123 Day 1	Pre-dose [b]	12 Lead
	Week 147 Day 1	Pre-dose [b]	12 Lead
	Week 171 Day 1	Pre-dose [b]	12 Lead
End of Treatment	EoT	Anytime	12 Lead (triplicate 12 lead if EoT before wk 15)
Follow-up	Last dosing + 105 days	Anytime	12 Lead
Unscheduled		Anytime	Triplicate 12 Lead

[a] The exact date and time of dosing must be recorded on the appropriate eCRF. The ECG assessments must be performed at the same timepoint as the PK timepoint. In case the PK timepoints are amended, the same amendment should apply to the ECG assessments.
[b] within 24hr before dose administration

Note: In order to ensure ECG evaluation is received from the central laboratory for eligibility assessment, it is advisable to perform the ECG at least 72 hours prior to the scheduled enrollment date.

In the event that a QTcF value of > 470 ms is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the time and date of the last study drug intake to determine the drug exposure (refer to Section 7.2.3). In case of QT prolongation, study drug should be discontinued until normalized as described in Section 6.3.1.2

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

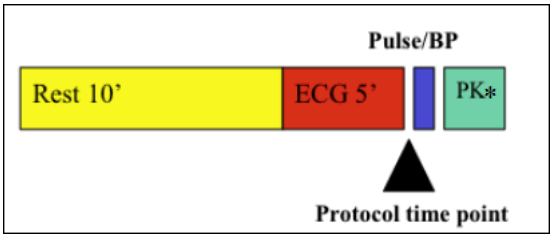
All ECGs collected during the study, including unscheduled safety triplicate ECGs with clinically relevant findings, should be transmitted to the central core ECG laboratory for review. The results of the centrally assessed ECGs are automatically transferred into the clinical

[redacted]

database. Any original ECG not transmitted to a central laboratory should be forwarded for central review and a copy kept in the source documents at the study site. Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), subject number, date, and kept in the source documents at the study site.

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

Timing of study procedures:



[redacted]

7.2.3 Pharmacokinetics, pharmacodynamics, and immunogenicity

Serial blood samples will be collected from all patients to assess PK and PD of crizanlizumab. Non-compartmental PK and PD parameters will be derived from each individual serum concentration- or inhibition-time profile using appropriate methods and software. Refer to Section 10.5.4 for a table of PK parameters that will be derived.

[redacted]

7.2.3.1 Pharmacokinetic, pharmacodynamic, and immunogenicity blood collection and handling

At specified time points described in Table 7-5, blood samples should be collected from the arm opposite from the investigational drug infusion into serum separator tubes. All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. 4.5 mL blood draws should be collected when PK and PD are specified. 8 mL blood draws should be collected when PK, PD and inmunogenicity (IG) samples are needed.

The blood samples will be allowed to clot for approximately 30 minutes at room temperature and then centrifuged for 10 minutes at approximately 3000g. Each serum sample will be aliquoted, and transferred into freezer-proof polypropylene screw-cap tubes (2 tubes for PK, 2 tubes for PD and 3 tubes for IG at each specified time points, at least 0.5 mL serum in each tube). The serum tubes will be frozen within 90 minutes of venipuncture and kept below -70°C in an upright position pending shipment and analysis.

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

Refer to the [CSEG101A2202 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of samples.

Table 7-5 Pharmacokinetic, pharmacodynamics and immunogenicity blood collection log

Week	Day	Scheduled timepoint following the initiation of infusion	PK collection number/Dose reference ID		PK sample No	PD sample No	IG sample No	Sample volume (mL)
1	1	Pre-dose	1	--	1	101	201	8
1	1	0.5h (± 5 min end of infusion)	1	--	2	--	--	2.5
1	1	1h (± 5 min)	1	--	3	--	--	2.5
1	1	2h (± 30 min)	1	--	4	102	--	4.5
1	1	4h (± 30 min)	1	--	5	--	--	2.5
1	1	6h (± 30 min)	1	--	6	--	--	2.5
1	2	24h (± 2 hr)	1	--	7	103	--	4.5
1	4	72h (± 2 hr)	1	--	8	104	--	4.5
2	1	8 days (± 24 hr)	1	--	9	105	--	4.5

[redacted]

Week	Day	Scheduled timepoint following the initiation of infusion	PK collection number/Dose reference ID		PK sample No	PD sample No	IG sample No	Sample volume (mL)
3	1	Pre-dose (± 24 hr[c])	2	101[a]	10	106	202	8
7	1	Pre-dose (± 24 hr[c])	3	201[a]	11	107	203	8
11	1	Pre-dose (± 24 hr[c])	4	301[a]	12	108	204	8
15[b]	1	Pre-dose (± 24 hr[c])	5	401[a]	13	109	205	8
15[b]	1	0.5h (± 5 min end of infusion)	5	--	14	--	--	2.5
15[b]	1	1h (± 5 min)	5	--	15	--	--	2.5
15[b]	1	2h (± 30 min)	5	--	16	110	--	4.5
15[b]	1	4h (± 30 min)	5	--	17	--	--	2.5
15[b]	1	6h (± 30 min)	5	--	18	--	--	2.5
15[b]	2	24h (± 2 hr)	5	--	19	111	--	4.5
15[b]	4	72h (± 2 hr)	5	--	20	112	--	4.5
16[b]	1	8 days (± 24 hr)	5	--	21	113	--	4.5
17[b]	1	15 days (± 24 hr)	5	--	22	114	--	4.5
18[b]	1	22 days (± 24 hr)	5	--	23	115	--	4.5
19[b]	1	Pre-dose [c]	6	501[a]	24	116	206	8
23	1	Pre-dose [c]	7	601[a]	25	117	207	8
27	1	Pre-dose [c]	8	701[a]	26	118	208	8
31	1	Pre-dose [c]	9	801[a]	27	119	209	8
35	1	Pre-dose [c]	10	901[a]	28	120	210	8
39	1	Pre-dose [c]	11	1001[a]	29	121	211	8
43	1	Pre-dose [c]	12	1101[a]	30	122	212	8
47	1	Pre-dose [c]	13	1201[a]	31	123	213	8
51	1	Pre-dose [c]	14	1301[a]	32	124	214	8
75	1	Pre-dose [c]	15	1401[a]	33		215	6
99	1	Pre-dose [c]	16	1501[a]	34		216	6
123	1	Pre-dose [c]	17	1601[a]	35		217	6
147	1	Pre-dose [c]	18	1701[a]	36		218	6
171	1	Pre-dose [c]	19	1801[a]	37		219	6
Follow up phase	1	---	20	1901[a]	38		220	6
Unscheduled Sample[d]		---	---		1001+	2001+	3001+	8

[a] For the PK pre-dose samples (sample number 10-13 and 24-38), the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose reference IDs as indicated in the above table.

[b] Sampling to occur at steady state (week 15). If dose is interrupted and an infusion is delayed before week 15, the steady state sampling will occur after the dose has been resumed and 3 consecutive infusions have been given without interruption.

[c] within 24hr before dose administration.

[redacted]

[redacted]

7.2.3.2 Analytical method

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

A pharmacodynamic marker of crizanlizumab is the *ex vivo* P-selectin inhibition measured by a surface plasmon resonance assay using human serum samples. Crizanlizumab in serum samples binds to spiked Psel-Ig (P-selectin coupled to Ig) and inhibits its binding to a PSGL1 peptide.

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

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

[redacted]

[redacted]

[redacted]

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 105 days (5 half-lives of crizanlizumab) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be

[redacted]

used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1-5)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted for the 7.5 mg/kg dosage only, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met
- Outcome (not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, 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.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

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

8.1.1.1 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. As VOCs are considered secondary endpoints for the purpose of evaluation of efficacy, 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.Vaso-occlusive crisis (including fatal outcomes), if documented by use of appropriate method and in accordance with the definition described in Section 7.2.1 of this protocol will not be reported as a serious adverse event to Novartis according to the requirements in Section 8.2 of this protocol. 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 8.1 and Section 8.2 and must be reported to Novartis within 24 hours of learning of the new information.

The events in Table 8-1 are the VOCs that will not be reported as AEs/SAEs.

Table 8-1 List of VOC Events Not Requiring AE/SAE Reporting

VOC Event
Uncomplicated sickle cell-related pain crisis (SCPC) or vaso-occlusive crisis (VOC)*
Acute chest syndrome
Hepatic sequestration
Splenic sequestration
Priapism requiring a visit to a medical facility

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

[redacted]

Adverse events of special interest are defined on the basis of an ongoing review of the safety data.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Note: fatal or life-threatening VOCs are not considered an SAE and should be recorded on the appropriate VOC eCRF page
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Vaso-occlusive crisis as defined in the protocol
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 105 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including 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 should be reported separately as a new event.

Any SAEs experienced after the 105 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically

[redacted]

thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug 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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology 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 study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

[redacted]

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol 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.

[redacted]

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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 EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The investigator must certify that the data entered into the eCase Report Form is complete and accurate, and that entry and updates are performed in a timely manner.

For PK, PD [redacted] samples, information about Treatment Periods, Visits, time points, and date and time of sample collection will be recorded on the eCRFs and also on the requisition forms sent to Central labs. A reconciliation of information regarding subjects and samples between the eCRF database and the lab database will be carried out by designated Novartis personnel (or designated CRO).

9.4 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 WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Any samples or data to be analyzed centrally (PK, PD, [redacted] central laboratory, central ECG reading) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and

[redacted]

accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics, the Global Head of Data Management and the Global Head of Clinical Development.

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

10 Statistical methods and data analysis

The analysis of study data for the primary clinical study report (CSR) will be based on all patient data up to the time after the primary PK and PD parameters are available for at least 27 patients for 5.0 mg/kg treatment group in the PAS1 and PDS1 respectively, or a total of 45 patients have been enrolled in the 5.0 mg/kg treatment group, whichever occurs first.

The additional data for any patients continuing to receive study drug past this time, as allowed by the protocol, will be further summarized in a final study report once these patients have completed or discontinued the study.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned and who received at least one dose of study treatment. Patients will be analyzed according to the crizanlizumab dose (5.0 mg/kg or 7.5 mg/kg) they have been assigned to.

10.1.2 Safety set

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the dose level received (5.0 mg/kg or 7.5 mg/kg), where dose level received is defined as the assigned dose level if the patient took at least one dose of that treatment or the first dose received if the assigned dose level was never received.

10.1.3 Pharmacokinetic analysis set

The Pharmacokinetic analysis set 1 (PAS1) includes all patients who provide at least one evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Patient receives the planned treatment of 5.0 mg/kg or 7.5 mg/kg before single dose PK profile or 3 consecutive doses of the planned treatment before the multiple dose PK profile
- Patient provides at least one primary PK parameter
- Patient does not have any transfusion of blood product in the last 4 weeks before the first PK sample of the full PK profile, or during the full PK profile

The Pharmacokinetic analysis set 2 (PAS2) includes all patients who receive at least one planned treatment of 5.0 mg/kg or 7.5 mg/kg and provide at least one corresponding evaluable PK concentration.

[redacted]

10.1.4 Other analysis sets

10.1.4.1 Pharmacodynamics analysis set

The pharmacodynamics analysis set 1 (PDS1) includes all patients who provide at least one evaluable PD profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Patient receives the planned treatment of 5.0 mg/kg or 7.5 mg/kg before single dose PD profile or 3 consecutive doses of the planned treatment before the multiple dose PD profile
- Patients provides at least one PD-AUC (single dose or multiple dose) parameter
- Patient does not have any transfusion of blood product in the last 4 weeks before the first PD sample of the full PD profile, or during the full PD profile

The pharmacodynamics analysis set 2 (PDS2) includes all patients who receive at least one planned treatment of 5.0 mg/kg or 7.5 mg/kg and provide at least one corresponding evaluable PD assessment.

10.1.4.2 Pharmacokinetic-Pharmacodynamics analysis set

The pharmacokinetic-pharmacodynamics analysis set (PKPDS) includes all patients in the Safety set who have at least one trough concentration or one p-selectin inhibition.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively by treatment group for all patients 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.

Relevant medical histories will be summarized by system organ class and preferred term.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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, minimum, and maximum will be presented.

The duration of exposure in days to study drug 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 patients with dose adjustments (interruption or permanent discontinuation) and the reasons will be summarized for all patients by treatment group and all dosing data will be listed.

[redacted]

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 Anatomical Therapeutic Chemical (ATC) classification system for all patients.

10.4 Primary objective

The primary objective is to characterize the PK and PD of crizanlizumab at 5.0 mg/kg in adult SCD patients.

10.4.1 Variables

The primary variables of the study are the PK and PD parameters after single dose and after multiple doses.

Primary PK parameters:

- AUCd15, AUCtau, Cmax

The remaining PK parameters will be analyzed as secondary variables.

PD parameters of crizanlizumab

- PD-AUCd15 after single dose
- PD-AUCd29 after multiple doses

10.4.2 Statistical hypothesis, model, and method of analysis

The inter-subject variations and CV% will be presented for the primary PK parameters. The point estimate and the corresponding two-sided 90% confidence interval (CI) for the mean of the log-transformed primary PK parameters after single dose and multiple doses will be derived respectively. The point estimate and CI will be anti-log transformed to obtain the point estimate and the 90% confidence interval for the geometric mean on the original scale.

The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented for all PK parameters defined in Table 10-1 except Tmax, where only n, median, minimum and maximum will be presented.

Table 10-1 Non compartmental pharmacokinetic parameters

AUCd15	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1) after single dose
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed serum drug concentration after dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) serum drug concentration after dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1)
T1/2	The half-life during a dose interval (time)

The PAS1 for 5.0 mg/kg treatment group will be used for all PK analyses described above.

[redacted]

Descriptive statistics for crizanlizumab concentration will be presented at each scheduled timepoint.

All individual concentration-time profiles for crizanlizumab with median will be displayed graphically on semi-log view after single and multiple doses respectively. In addition, the mean (+/- SD) and geometric mean concentration-time profiles over time will be displayed graphically on the linear and semi-log view.

All individual PK parameters and PK concentration data for crizanlizumab will be listed.

All individual pre-dose concentrations for crizanlizumab with median will be displayed graphically on semi-log view over time. In addition, the mean (+/- SD) and geometric mean pre-dose concentrations over time will be displayed graphically on the linear and semi-log view.

The PAS2 for 5.0 mg/kg treatment group will be used for these PK analyses.

PD-AUCd15 and PD-AUCd29 will be derived from the P-selectin inhibition data of week 1 and week 15, respectively. The point estimate and the corresponding two-sided 90% CI for the mean of the log-transformed PD-AUC after single dose and multiple doses will also be provided. The point estimate and CI will be anti-log transformed to obtain the point estimate and the 90% confidence interval for the geometric mean on the original scale.

The PDS1 for 5.0 mg/kg treatment group will be used for all PD analyses described above.

Descriptive statistics for PD inhibition will be presented at each scheduled timepoint.

All individual PD-time profiles with median will be displayed graphically on semi-log view after single and multiple doses respectively. In addition, the mean (+/- SD) and geometric mean PD-time profiles over time will be displayed graphically on the linear and semi-log view.

All individual PD parameters and PD data will be listed.

Median pre-dose inhibition will be displayed graphically on semi-log view over time. In addition, the mean (+/- SD) and geometric mean pre-dose inhibition over time will be displayed graphically on the linear and semi-log view.

The PDS2 for 5.0 mg/kg treatment group will be used for these PD analyses.

10.4.3 Handling of missing values/censoring/discontinuations

Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

Below the limit of quantitation (BLQ) values will be set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. BLQ values will be treated as missing for the calculation of the geometric means and geometric CV%.

Missing values for the PD parameter or data will not be imputed and will be treated as missing.

10.4.4 Supportive and Sensitivity analyses

Details will be provided in the Statistical Analysis Plan.

[redacted]

10.5 Secondary objectives

The secondary objectives in this study are to assess the efficacy, safety and tolerability of crizanlizumab at 5.0 mg/kg and 7.5 mg/kg in SCD patients. The FAS will be used for all analyses.

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

The following endpoints will be summarized descriptively by treatment group.

- Annualized rate of VOC events leading to healthcare visit in clinic/ER/hospital
- Annualized rate of VOC events treated at home, based on documentation by health care provider following phone contact with patient
- Annualized rate of all VOC events (including both healthcare visit and home treatment)
- Annualized rate of each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism)
- Annualized rate of hospitalizations and ER visits (both overall and VOC-related)
- Annualized days of hospitalizations and ER visits (both overall and VOC-related)

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All safety data will be summarized by treatment group.

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

1. pre-treatment period: from day of patient'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 106 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

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 by treatment group.

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.

[redacted]

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.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. 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.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology and biochemistry tests by treatment group:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03,

- 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 [redacted] 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.

10.5.3.4 Other safety data

ECG

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

The number and percentage of patients with notable ECG values will be presented. In addition, a listing of these patients will be produced.

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

[redacted]

10.5.3.5 Supportive analyses for secondary objectives

Any supportive analyses that are considered appropriate for secondary variables will be described in the SAP prior to DBL.

10.5.3.6 Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number of treatment dose interruptions. Reasons for dose interruption will be listed by patient and summarized by treatment group.

10.5.4 Pharmacokinetics

Please refer to Section 10.4.

[redacted]

10.5.6 Resource utilization

Not applicable.

10.5.7 Patient-reported outcomes

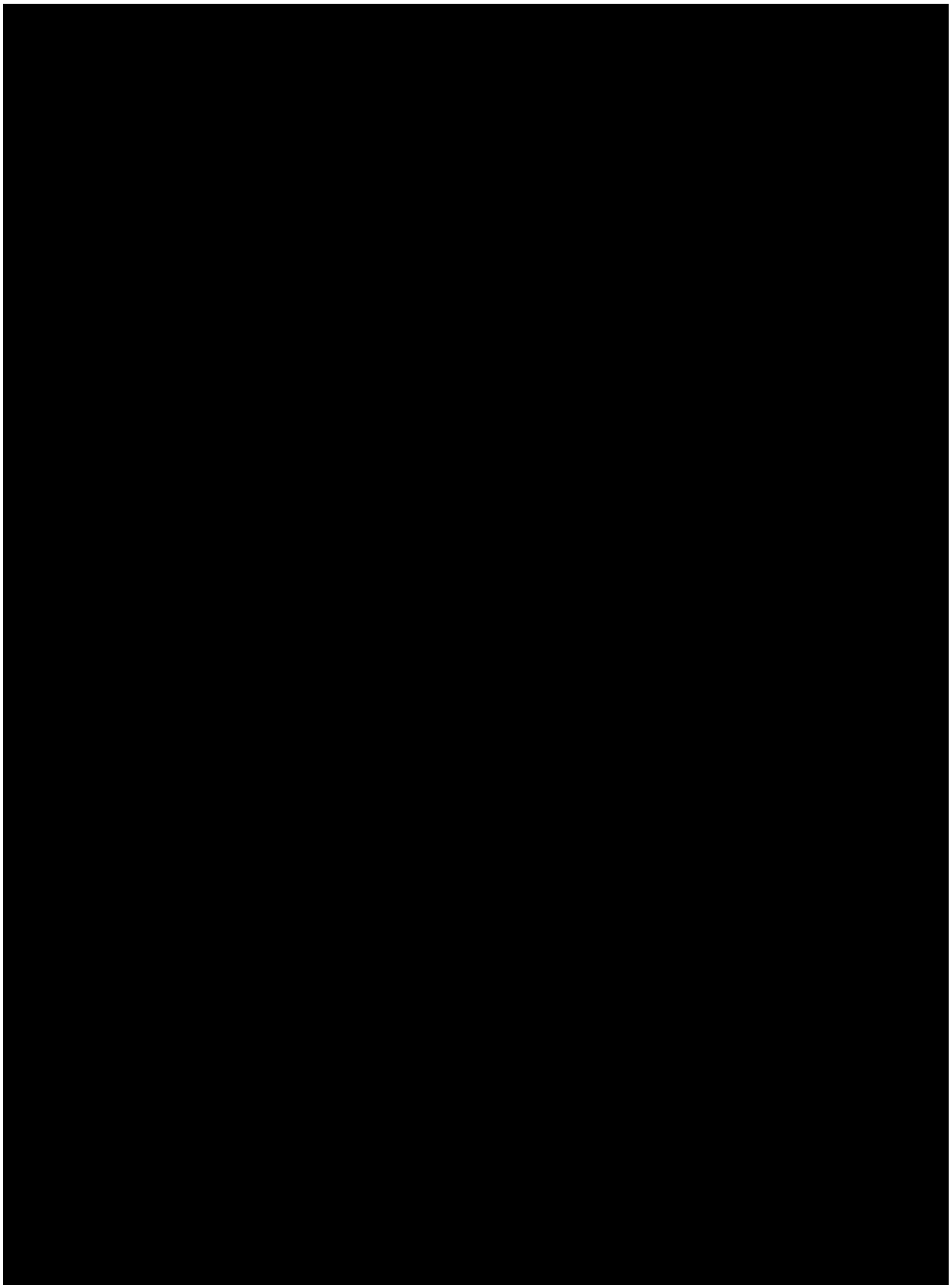
Not applicable.

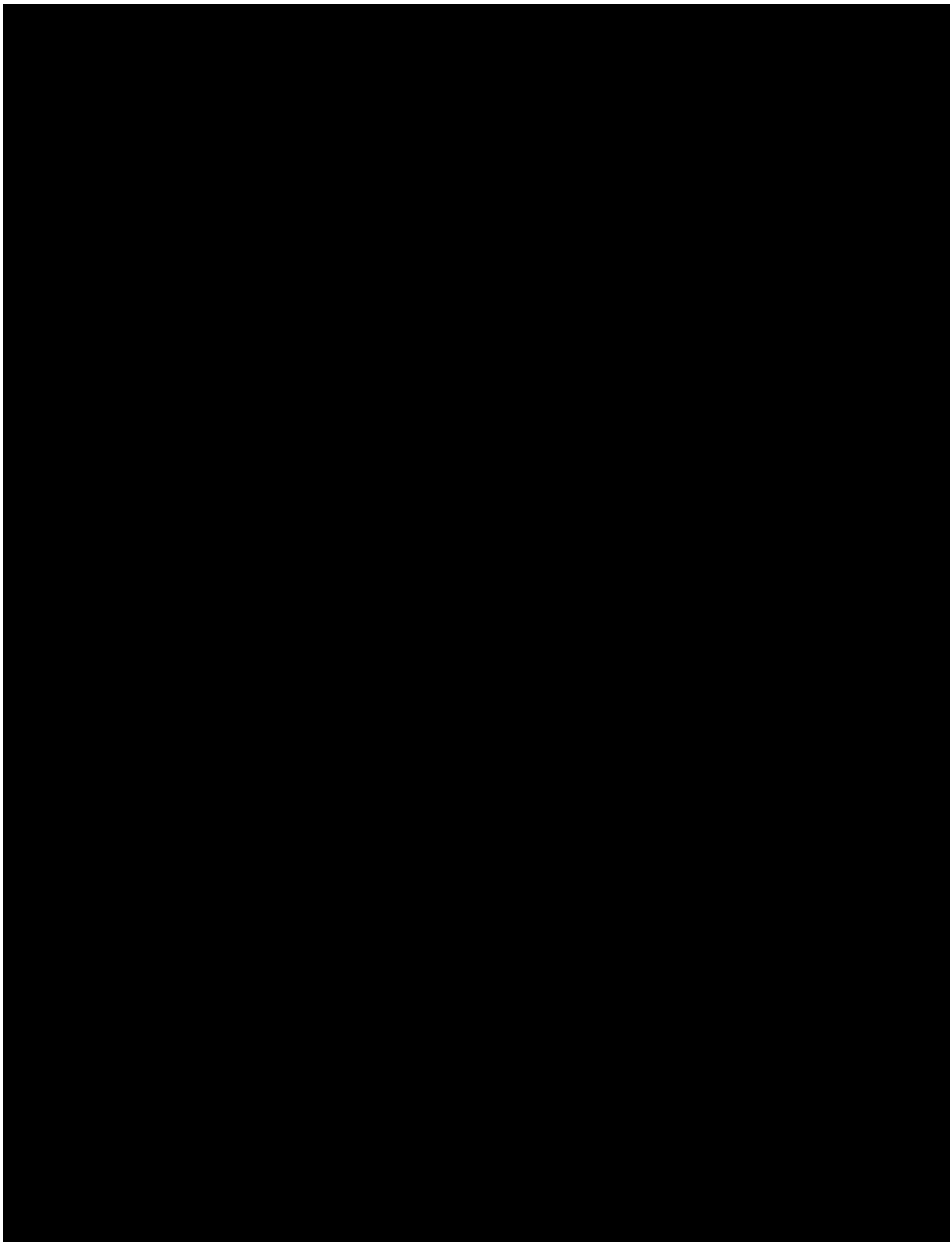
10.5.8 Immunogenicity

Immunogenicity will be characterized descriptively tabulating antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment.

[redacted]

[redacted]





10.7 Interim analysis

An interim analysis may be performed when there are at least 27 patients with single dose evaluable PK profiles and approximately 5 patients with both single dose and multiple dose evaluable PK profiles in the PAS1 for 5.0 mg/kg treatment group. Point estimate and 90% confidence intervals for the primary PK parameters will be calculated. PopPK modeling will be performed. Another interim analysis may be performed when there are approximately 15 patients with multiple dose evaluable PK profiles in the 5.0 mg/kg treatment group in the PAS1. Should the criteria for the two interim analyses be reached at similar times compatible with both objectives, a single combined interim analysis will be performed. Additional earlier or later ad hoc interim analyses of PK/PD/safety may be performed in order to support potential health authority requests.

10.8 Sample size calculation

5.0 mg/kg treatment group:

For sample size consideration, PK and PD data from Study CSEG101A2101 and study CSEG101A2201 were used. Currently, the inter-subject variability of PK parameters, such as AUC and Cmax, of VOC patients is not known and needs to be approximated from the Ctrough results of patient study A2201. In that study the inter-subject variability of Ctrough was found to be 50.8%.

Data of study A2101 has revealed a high correlation between PK concentrations 336h post-dose and AUCt. Assuming this correlation holds true for patients together with the assumption of an

inter-subject CV = 50.8% of pre-dose concentrations allows an approximation of expected inter-subject CV = 46.1% for AUCt.

Currently, the inter-subject variation of the P-Selectin inhibition at 5.0 mg/kg and the respective PDAUC672hr is not known. However, approximations utilizing results from lower dose groups tested in study CSEG101A2101 suggest an inter-subject coefficient of variation of approximately CV = 34.1%.

When the sample size is 27 evaluable patients, a two-sided 90% confidence interval for a single mean of log-transformed AUC will extend 0.140 from the observed mean, ensuring a precision of 15%, assuming that the standard deviation is known to be 0.439 and the confidence interval is based on the large sample z statistic.

Similarly, with the same sample size of 27 evaluable patients, a two-sided 90% confidence interval for a single mean of log-transformed PD-AUC will extend 0.105 from the observed mean, representing a precision of about 11%, assuming that the standard deviation is known to be 0.332 and the confidence interval is based on the large sample z statistic.

After the start of trial A2202, new information was made available through the single dose HV study CSEG101A2102, in which PK variability for SEG101 was lower than for SelG1. Using the same process as described above, but this time starting from the CV% in A2102 SEG101 rather than A2101 SelG1, leads to the CV% for AUCt in patients being projected to be 34.7%, instead of 46.1%.

With such assumption for a lower CV%, a smaller sample size of 15 patients would be sufficient to ensure the same precision as originally expected with 27 evaluable patients: with 15 evaluable patients, a two-sided 90% confidence interval for a single mean of log-transformed AUC will extend 0.143 from the observed mean, still ensuring a precision of 15%, assuming that the standard deviation is known to be 0.3369 and the confidence interval is based on the large sample z statistic.

However, considering the uncertainties around variability estimations (projected based on a single-dose HV study rather than directly observed in a multiple-dose patient study), the sample size of 27 for the primary analysis is maintained and an interim analysis will be conducted on 15 evaluable patients.

Exploratory 7.5 mg/kg treatment group:

When the sample size for this dose group is 6, a two-sided 90% confidence interval for a single mean will extend 0.172 from the observed mean, assuming that the standard deviation is known to be 0.209 and the confidence interval is based on t-statistic.

Considering a drop-out rate of 35% from the CSEG101A2201 study, and to account for the heterogeneity of patients in terms of genotype and renal function, the multiplication factor for enrollment versus evaluable patients is 67%, and 45 patients will need to be enrolled in the 5.0 mg/kg treatment group. The same holds for the exploratory cohort, requiring enrollment of 10 patients to yield 6 evaluable patients at the 7.5 mg/kg dose.

10.9 Power for analysis of key secondary variables

Not applicable.

[redacted]

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. 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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

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

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication 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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. wwwclinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on wwwnovartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (wwwicmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to wwwnovartiscom.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept

at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

[redacted]

12.1 Amendments to the protocol

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/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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14 Appendices

14.1 Appendix 1 – List of prohibited CYP3A inhibitors and inducers

The list of prohibited CYP3A inhibitors and inducers is provided in Table 14-1 (this list may not be comprehensive).

Table 14-1 List of prohibited CYP3A inhibitors and inducers

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
clarithromycin	amprenavir	carbamazepine *	felbamate *
conivaptan	aprepitant	phenobarbital *	topiramate * (>200 mg/day)
indinavir	atazanavir	phenytoin *	oxcarbazepin *
itraconazole	cimetidine	fosphenytoin *	eslicarbazepin *
ketoconazole	ciprofloxacin	primidone *	rufinamide *
lopinavir	darunavir	avasimibe	bosentan
mibefradil	diltiazem	rifabutin	efavirenz
nefazodone	elvitegravir	rifampin	etravirine
nelfinavir	erythromycin	St. John's Wort	modafenil
posaconazole	fluconazole		nafcillin
ritonavir	grapefruit juice		ritonavir
saquinavir	schisandra sphenanthera		talviraline
telithromycin	tipranavir		tipranavir
troleandomycin	tofisopam		
voriconazole	verapamil		

* These drugs are Enzyme Inducing Anti-Epileptic drugs.
This database of CYP inhibitors and inducers was compiled from the Indiana University School of Medicine's
"Clinically Relevant" Table, from the University of Washington's Drug Interaction Database based on in vitro studies and from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche 2008).

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14.2 Appendix 2 – List of prohibited QT-prolonging drugs

All QT-prolonging drugs listed in Table 14-2 are prohibited for all subjects from screening through permanent discontinuation of study. Table 14-2 lists drugs with a known risk for TdP as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP.

Table 14-2 List of prohibited QT prolonging drugs

Drug	QT risk(*)	Comment
Amiodarone	Known risk for TdP	Females>Males, TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given i.v. or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
(*)Classification according to the Qtdrugs.org advisory board of the Arizona CERT Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme. Note: drugs with a known risk for TdP that are also moderate or strong inhibitors of CYP3A mentioned		

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