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Novartis Research and Development

SEG101

Clinical Trial Protocol CSEG101A2301/ NCT03814746

A phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab versus placebo, with or without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients with Vaso-Occlusive Crises (STAND)

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Table of contents

List of tables

List of figures

List of abbreviations

Ab	antibody
AC	Adjudication Committee
ACR	albumin creatinine ratio
ACS	acute chest syndrome
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
APC	Acute Pain Crisis
[redacted]	[redacted]
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under curve
AUC0-t	area under the concentration-time curve to a defined point of time
AUCinf (AUC0-∞)	area under the concentration-time curve extrapolated to infinity
AUClast	area under the curve calculated to the last measurable concentration point
AV	Atrioventricular
BIL	Bilirubin
BUN	Blood Urea Nitrogen
C3a	Complement component 3a
C5a	Complement component 5a
CFR	Code of Federal Regulation
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
CMO & PS	Central Monitoring Operations & Patient Safety
CMV	Cytomegalovirus
COVID-19	Coronavirus disease of 2019
CPO	Country Pharma Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DAR	dose administration record
DDE	direct data entry
DILI	drug-induced liver injury

DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EDTA	ethylenediamine tetraacetic acid
e.g.	for example
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of treatment
ER	emergency room
eSAE	Electronic Serious Adverse Event
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FWER	family-wise type I error rate
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
h	Hour
HA	Health Authority
Hb	Hemoglobin
HbF	fetal hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV-DNA	hepatitis B virus - deoxyribonucleic acid
hCG	human chorionic gonadotrophin
HCV	hepatitis C
HCVAb	hepatitis C virus antibody
HDL	high density lipoproteins
HIV	human immunodeficiency virus
HIV Ab	human immunodeficiency virus antibody
HPLC	high performance liquid chromatography
HR	hazard ratio
HSV	herpes simplex virus
HU/HC	hydroxyurea/hydroxycarbamide
IB	Investigator Brochure
[redacted]	[redacted]
ICF	Informed consent form

ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IG	Immunogenicity
IL	Interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
IV	Intravenous
LDL	low density lipoproteins
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPT	low platelet count
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram(s)
[redacted]	[redacted]
mL	milliliter(s)
mPAP	mean pulmonary arterial pressure
NCA	non-compartmental analysis
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
ORN	Off-site Research Nurse
OTC	over the counter
PAP	pulmonary arterial pressure
PAS	pharmacokinetic analysis set
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PDS	pharmacodynamics analysis set
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic
PROs	patient reported outcomes
Psel-Ig	P-selectin coupled to Ig
PSGL-1	P-selectin glycoprotein ligand-1

PT	prothrombin time
q4w	every 4 weeks
QMS	Quality Management System
[redacted]	quality of life
QTcF	Fridericia's Correction Formula
R Value	ALT/ALP in x ULN
RBC	red blood cell(s)
RNA	ribonucleic acid
ROW	rest of the world
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Steering Committee
[redacted]	[redacted]
SCD	Sickle Cell Disease
[redacted]	[redacted]
SD	standard deviation
SEG101	Novartis humanized anti-P-selectin monoclonal antibody variant
SelG1	Reprixys humanized anti-P-selectin monoclonal antibody variant
SOP	standard operating procedure(s)
SUSAR	Suspected Unexpected Serious Adverse Reactions
$T_{1/2}$	half-life during a dose interval (time)
[redacted]	[redacted]
TBIL	total bilirubin
TEAE	Treatment-emergent adverse events
TBV	Total Blood Volume
TFQ	Trial Feedback Questionnaire
Tmax	time to reach maximum concentration
TNF-a	tumor necrosis factor alpha
TRV	tricuspid regurgitant jet velocity
ULN	upper limit of normal
US	United States
USD	United States dollar
[redacted]	[redacted]
VOC	vaso-occlusive crisis
Vwf	von Willebrand factor
Wk	week(s)
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Investigational treatment	The investigational drug whose properties are being tested in the study as well as their associated treatment control (placebo). Investigational treatment does not include other treatments (p.e HU/HC and L-Glutamine) administered as concomitant background therapy allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home
Off-site healthcare Professional	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs

(OHP)	certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest for the study
Participant	A trial participant (patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Study Completion	Point/time at which the participant came in for a final evaluation visit or when study drug was discontinued whichever is later
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Study treatment	Any investigational treatment administered to the participant as part of the required study procedures
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial
Study treatment interruption	Dose administration that cannot be made as per protocol and the infusion is fully skipped
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Withdrawal of study consent (WoC) / Opposition to use data / biological samples	Withdrawal of consent from the study occurs only when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent

Amendment 5 (05-Mar-2021)

Amendment rationale

At the time of this amendment, 186 participants have been enrolled into the study.

The primary purpose of this amendment is:

- to specify that, as per HA feedback and EMA guideline (2017) for trial related blood loss in the adolescent population, the volume of blood to be taken in adolescents with body weight ≤ 45kg, will not exceed 1% of the total blood volume (TBV) per single time and will be no more than 3% of TBV in a 4 weeks period. Consequently, hematology/biochemistry, PK, pharmacogenomic [redacted] parameters and/or the time points at which they are collected are adapted

- to clarify that participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete the 105 days post-treatment follow-up. Exception will be made if treatment discontinuation occurred before end of week 52, the monthly phone calls up to 1 year after first treatment will be required. If the participant will continue crizanlizumab beyond the EOT visit, via commercial supply or post-trial access, the assessments requested at EOT visit will have to be performed prior to next crizanlizumab infusion. For participants discontinuing from study treatment prior to completion of W259D1 visit and continuing under crizanlizumab outside the study, and for all participants completing the W259D1 visit whether they continue on crizanlizumab outside the study or not, EOT visit should be completed 28 days +/-7 days from the last dose

- to provide with the mitigation plan during ongoing or future Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster

Changes to the protocol

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

- The following Sections and Tables, as per the per HA feedback and EMA guideline (2017) for trial related blood loss in the adolescent population to ensure that the volume of blood to be taken in adolescents with body weight ≤ 45kg will not exceed 1% of the total blood volume (TBV) per single time and will be no more than 3% of TBV in a 4 weeks period, are updated:

-Table 8-1: W15D2 visit is added. The collection of Hematology, Chemistry and Coagulation samples for adolescents with body weight ≤ 25kg is transferred from W15D1 to W15D2

-Table 8-1 COVID-19 Ab samples for adolescents with body weight ≤ 25kg should be collected separately from safety samples at Screening visit and collection should stop after W23D1

-Table 8-1 Pharmacogenetic sample collection: removed for adolescents with body weight ≤ 45kg

-Table 8-6: collection of W1D1 PD 2h sample number 102, W16D1 PD sample number 113, W18D1 PD sample number 115 and W19D1 IG sample number 204 is removed for adolescents with weight ≤ 25 kg

[redacted] Pharmacogenetic sample collection is removed for adolescents with body weight ≤ 45kg

- The following Sections and Tables, in order to clarify that participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete the post-treatment follow-up, are updated: Table 2-1; Section 3 Study design and Post-Treatment Follow-up; Section 6.2.1 (in addition, safety follow up visit is replaced with last protocol visit); Section 6.5.2; Section 8; Table 8-1; Table 8-3; Section 9.1.1; Section 9.2; Section 10.1.1 and Section 10.1.3

- Table 8-1 and Section 9.1.1, to clarify that EOT visit should be completed 28 days +/-7 days from the last dose, is updated

- The following sections, to clarify that if the participant will continue crizanlizumab beyond the EOT visit, via commercial supply or post-trial access, the assessments requested at EOT visit will have to be performed prior to next crizanlizumab infusion, are updated: Table 8.1; section 8 and 9.1.1

- Updates to align with the latest Novartis Global Clinical Trial Protocol Template v4.0 (15-Feb-2021) are in following Tables and Sections: Glossary of Terms, Exclusion criteria 8, Table 6-2; Sections 6.4; 9.1.1; 9.1.2; 9.1.3 and 13-5

The rest of updated Sections and Tables are listed below:

- Section 1.1.2.1: update of the approval status in the US and worldwide

- Section 4-6: addition of the new section “Rationale for Public Health Emergency mitigation procedures”, as per global template

- Section 6.2.1: since the current safety profile did not show safety concerns, clarification that anti-platelets agents or anticoagulants at doses targeting therapeutic levels should be used with caution

- Section 6.2.1.1: clarification that anti-platelets agents or anticoagulants at therapeutic doses should be used with caution due to a potential effect of P-selectin inhibition on hemostasis

- Table 6-3: clarification that in case of Grade 2 IRR the interruption of infusion should be “temporary”

- Section 8: addition, as per global template, of alternative methods of providing continuing care if on-study visits are limited or prevented during a Public Health emergency as declared by Local or Regional authorities

- Table 8-1: addition of IRR testing and instruction that IRR eCRF page should be completed if infusion related reaction is reported as such in the AE eCRF page
- Section 8.1, 8.4.1 and Tables 8-1 and 8-4: clarification that, local sampling for platelet count test will be performed throughout the trial for adolescents with body weight > 45kg and adults
- Table 8-6: PK sample number 15 and footnote "c" for pre-dose samples at EOT visit are removed
- Section 8.6: additional information added to bring more clarity to Off-site research nursing visits
- Section 10: as per global template, replacement of COVID 19 pandemic with " during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster " . In addition, the word will is replaced with can, "it is safe" is added to read: ...regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe the participant visit the site again.
- Section 12.5.2: Clarification added regarding the definition of the on-treatment and post-treatment periods
- Section References: reference "Ethical considerations for clinical trials on medicinal products conducted with minors, 2017" is added

Various administrative and spelling corrections made throughout the protocol.

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.

Summary of previous amendments

Amendment 4 (04-Nov-2020)

Amendment rationale

At the time of this amendment, 120 participants have been enrolled into the study.

The primary purpose of this amendment is:

1. In order to allow adequate opportunity for enrollment into each of the four strata (the four possible combinations of the stratification factors), and avoid over-representation of any individual stratum, a capping of 90 adult participants per stratum will be implemented.

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.

- Section 3: Clarification added that a cap of 90 adult participants (adults defined as ≥ 18 years) will be implemented into any individual stratum.
- Section 4.5: the following language was added to summarize data on IRR and pain events, "In summary, current data suggest that administration of crizanlizumab can be commonly associated with infusion related reactions, including pain events, some of which can be severe and/or require hospitalization."
- Section 5 Study Population: the following language was added to create a cap on adult participants into each stratum: A capping of 90 adult participants per stratum will be implemented (Section 3).
- Section 6.4 Treatment Blinding: the word "unblinded" has been added for clarity.
- Section 7 Informed Consent Procedures: administrative changes for spacing issues.
- Section 8.1 Screening: the following text has been removed, "the 28 day screen period does not apply to the informed consent process." This sentence may be misinterpreted as screening starts the moment informed consent is fully signed.
- Table 8-1: Included immunoglobulins to the analysis of IRRs. Immunoglobulin added to footnote 24.
- Section 8.3.1 Efficacy Assessment: The following text was added: "as defined below" for clarity.
- Section 8.4.2 Electrocardiogram (ECG): the following duplicative text was removed for clarity, "ECG assessments will be conducted as outlined."

[redacted]

- Table 8-6: Administrative updates to add dose reference ID to the follow-up PK and align sample numbers for footnote c.
- Various administrative and spelling corrections made throughout the protocol.

Amendment 3 (28-Jul-2020)

Amendment rationale

At the time of this amendment, 88 participants have been enrolled into the study.

The primary purpose of this amendment is described below:

1. To introduce a new definition of acute pain crises (APCs) leading to healthcare visit; to define and collect data of those acute events leading to healthcare visit that do not meet the definition of VOC in terms of analgesic used per protocol. As a result, APCs leading to healthcare visit will also be reviewed and evaluated by an Adjudication Committee (AC).
2. To supplement the data collected on prior use of hydroxyurea/hydroxycarbamide (HU/HC) by adding reason for discontinuation as part of participant demographics as requested by the European Medicine Agency (EMA).
3. To provide additional guidance on how to manage infusion-related reactions (IRRs), e.g. with regard to
   - use of pre-medication as prophylaxis
   - caution in the use of steroids
   - slowing/reduction of infusion rate
4. To update blood sample collection based on current data that suggest that administration of crizanlizumab can be associated with IRRs, including pain events, some of which can be severe and/or require hospitalization. In order to better characterize these IRRs, blood samples will be collected pre-dose and post-dose at different time points and analyzed for cytokines, complement analytes and tryptase.
5. To update the risks and benefits of treatment with crizanlizumab to reflect the most recent available clinical data described in the latest edition of the Investigator's Brochure (Edition 10, released on 12-May-2020).
6. To provide guidance on the option of having certain protocol procedures performed at an off-site location by a qualified Research Nurse.
   - The existing protocol language that allows off-site Research Nursing visits to occur after one year of treatment has been further defined. Investigators can only offer this option to their participants if they meet certain eligibility criteria, if local regulations allow, and if the investigator, the participant, the parent(s)/legal guardian(s) (if applicable), and Novartis agree.

7. To add blood sample collection to allow for testing for COVID-19, in light of the COVID-19 pandemic and potential interaction with efficacy and safety assessments.
   - Language is included to address COVID-19-related changes to trial conduct and allow some flexibility when needed. Recommendations for handling of study treatment in case of active or suspected COVID-19 infection are added.
8. To remove pharmacodynamics (PD) sample collection beyond week 51 since there was no time-dependent PD observed in previous SEG101 studies. Since PD data up to week 51 is obtained when possible in other SEG101 studies, a similar period is implemented for this study.

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: Reference to "subject" or "patient" replaced with "participant" when referring to trial participant, to align with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
- Throughout: Use of acronym "APC" to reference "acute pain crises"
- Throughout: Typographical and grammatical errors addressed
- List of abbreviations: Updated by adding new abbreviations used across the protocol
- Glossary of terms: Updated to align with the last latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020) and include all terms referenced in the protocol
- Protocol Summary: Updated in alignment with the modifications made in the protocol sections

[redacted]

- Figure 3-1: Updated to correct grammatical errors, and references of "patient" or "subject" to "participant"
- Section 4.5: Added language regarding the potential risks of hemorrhages, infections, IRRs and immunogenicity in line with the latest edition of the Investigator's Brochure (Edition 10, released on 12-May-2020).
- Section 5: Aligned wording with protocol summary, specifying SCD patients who are not planning to initiate HU/HC or L-glutamine during the first year of investigational treatment can participate in this study
- Section 5.1 and 5.2: Suffix "a" added to the numbers of inclusion/exclusion criteria that had been changed with Protocol Amendment 1 (unintentionally omitted in Amendment 1)
- Section 5.2: Exclusion criterion #8 clarification added for contraception methods per local regulations
- Section 6.2.1.1: Added that prophylactic pre-medication is permitted and steroids should be used with caution for acute pain management in SCD patients
- Section 6.3.1: Additional information included for participants who are re-screened

- Section 6.5.1: Recommendations added for handling of study treatment in case of active or suspected COVID-19 infection
- Table 6-3:
  - Throughout: for consistency, instances of "maintain dose level" updated to "continue study treatment"; and instances of "discontinue the subject from the study" updated to "discontinue study treatment"
  - Isolated ALT Elevation: language updated to align across the studies of the clinical program
  - Combined elevations of ALT and bilirubin: language updated and reference to "in the absence of cholestasis" removed to align across the studies of the clinical program
  - Infusion-related reactions: criteria updated to provide further guidance
  - Footnote c deleted as a result of removing "in the absence of cholestasis"
- Section 6.5.2: Added that in case of a grade 3 or 4 IRR, additional blood samples will be collected
- Section 6.5.2.1:
  - Clarified that clinical information should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities for drug-induced liver injury
  - Reference to "in the absence of cholestasis" removed to align across the studies of the clinical program
- Section 7: Included the title and description of all informed consent documents which are utilized for the study to align with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
- Section 8:
  - Added "virtual contact" as a means for communication between the site staff and participant (or designee)
  - +/- 10 days visit window for the Follow-up in case of treatment discontinuation before end of Week 52 has been updated from treatment interruption
- Table 8-1:
  - Removed "Cycle" header and 0.5h and 2h post-dose time points as these are not needed
  - Added assessment "Optional Informed Consent Form for Off-site Research Nursing Visits"
  - Added assessment "COVID-19 testing" and corresponding footnote 23
  - [redacted]
  - Removed Prior/concomitant medications - HU/HC - L-glutamine as this line was redundant
  - Added Week information for End of Treatment visit and Monthly Follow Up
  - Footnote 17 reworded for clarity, referring to APCs separately from the categories of VOCs

  - Footnote 22 reworded for clarity, referring to APCs separately from the categories of VOCs
- Section 8.2: Updated to specify that prior use of HU/HC and reason for discontinuation will be collected as part of participant demographics
- Section 8.3.1:
  - Added clarification and additional information for definition of other APCs managed at home and those leading to healthcare visit
  - Removed wording which states that APCs managed at home (reported >24 hours) and entered in the CRF will not be counted as an APC
  - Removed reference to study participation card which is not required globally
  - Modified text to state that grouping of VOC and APC events which occur within 7 days of preceding event be based on clinical presentation and/or location
  - Recommendations added for COVID-19 testing if participant experiences a VOC/APC
- Table 8-4: Added "COVID-19 Ab" under the *Additional Tests* category, as well as corresponding footnote
- Table 8-5: Added footnote c to provide instructions for ECG collection when steady-state is not achieved at Week 15 Day 1
- Section 8.5.2.1 updated to clarify that serum samples are to be frozen and kept at -70°C in an upright position until shipment and analysis
- Table 8-6
  - Removed PD sample collections beyond week 51 to align across the studies of the clinical program
  - Added PK sample collection at Follow-up (Last Infusion +105 days) to align with IG sampling
  - Clarified 2hr PK/PD sampling requirements in footnote g
- Section 8.5.3:
  - Added that in case a participant has a grade 3 or grade 4 IRR, an additional sample should be collected
  - [redacted]
  - [redacted]
  - [redacted]
- Added Section 8.6 on "Participant Off-site research nursing visits" to provide more information on what the requirements are in order to offer Off-site research nursing visits to participants

- Section 9: Section headings aligned with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
- Section 9.1.1:
  - Added APCs to data being collected during follow-up phone calls for participants who discontinue treatment during the first year
  - Further guidance provided for contacting the IRT in case of treatment discontinuation
  - Further guidance provided for cases in which treatment is discontinued because the treatment code has been broken
- Section 9.1.2: Wording aligned with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
- Section 10: Language added to cover COVID-19 pandemic and maintenance of virtual/phone contacts with the participants for safety monitoring and discussion on participant's health in case on-sites visits cannot be performed
- Section 10.1.2: Added reference to the ICH-E2D Guidelines for "medically significant" events
- Section 10.1.4: Additional wording added to align with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020) and clarify that in case of pregnancy, study treatment must be stopped and pregnancy consent form read and signed by the participant
- Section 10.2.2: DMC assessment criteria corrected to remove "critical efficacy variables"
- Section 10.2.4: Added APCs leading to healthcare visit as a criteria for review and confirmation by the Adjudication Committee
- Section 10.3: Clarification that VOC/APC events suspected to be related to study treatment, and/or resulting in a fatal outcome, will be reported as AE/SAE in addition to the VOC/acute pain crisis eCRF page
- Section 11.2:
  - Included additional data points which are tracked in IRT to align with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
  - [redacted]
- Section 12.4.1: Clarified VOCs "leading to healthcare visit" will be reviewed and confirmed by an Adjudication committee
- Section 12.5.1: Removed the reference to Pharmacodynamic in the section heading, as PD is discussed in Section 12.5.4

[redacted]

[redacted]

IRBs/IECs

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

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Amendment 2 (02-Jun-2020)

Amendment rationale

At the time of this amendment, 81 patients have been enrolled in the study.

Amendment 2 is required to implement specific feedback received from the Medicines & Healthcare products Regulatory Agency (MHRA) upon review of the Amendment 1 dated 12-Feb-2020.

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.

- Table 6-3 and Section 6.7: Initial protocol wording reinstated for Grade 3 infusion-related reactions. Recommendation updated from temporary interruption of study treatment to permanent discontinuation of study treatment. Change mandated by MHRA.

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Amendment 1 (12-Feb-2020)

At the time of this amendment, 46 patients have been enrolled in the study.

The primary purpose of this amendment is described below:

1. To clarify in the objectives, endpoints and statistical analysis section:

- The annual rate of all VOCs (leading to healthcare visit and treated at home) will also be evaluated as a long term objective on the entire study period (on top of the key secondary endpoint focusing on the first year of treatment)

- VOCs managed at home will not only be analyzed as part of the key secondary endpoint, but also as part of a stand-alone secondary endpoint on annualized rate of VOCs managed at home.
- The secondary objective originally called "number of days with VOCs leading to healthcare visit" was renamed into "duration of VOC leading to healthcare visit", as it is a clearer name, in line with how this endpoints was actually defined in the original protocol Section 12.5.

2. To clarify definition and duration of the different VOCs as well as the definition of other acute pain crises (APCs) managed at home.

In addition, to minimize potential confounding effect with investigational treatment on efficacy endpoints, requirements for the use of approved therapies to treat SCD prior to study entry have been clarified in the inclusion criteria #5.

Updated safety information, consistent with the Investigator's Brochure Edition 9 (released on 17-May-2019), has been added.

Sections related to the study treatment preparation, dispensation, accountability and timing have been updated. Some details have been removed and reference to the Pharmacy Manual has been added instead.

It has been clarified that local laboratory re-sampling for platelet count is allowed at any time in case of clumping or other issues reported from the central laboratory.

Exclusion criteria #12 has been revised to exclude hospitalizations within 7 days prior to Week 1 Day 1 dosing instead of prior to screening for consistency with updated inclusion criteria #4.

Exclusion criteria #22 'Received prior treatment with crizanlizumab or other selectin targeting agent' has been added as required by the HA as well as the prohibition to use approved crizanlizumab or other selectin targeting agents during the entire study duration.

The Assessment Schedule has been updated to remove assessments that are no longer needed according to known safety profile of crizanlizumab. Other assessments have been entered and changes in format have been made for consistency with the CRF and Database (refer to changes to Table 8-1 described below).

The ECG collection plan has been updated to remove several ECG measures no longer needed since no effect of crizanlizumab on QT was identified.

PRO related sections have been updated to align with the new template text provided by PRO Center of Excellence at Novartis.

The number of consecutive doses to reach steady state sampling has been updated to 3 as confirmed by latest data.

The statistical section has been updated in line with the endpoints clarifications mentioned above and the final SAP.

Other minor corrections are also applied throughout the protocol.

Changes to the Protocol

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

- Throughout: typographical and grammatical errors addressed
- List of abbreviations: EOS (end of study) removed as not applicable to the study. HA (Health Authority) and mPAP (mean pulmonary arterial pressure) were added.
- Glossary of terms: "Cycles" removed as not applicable to the study, "Study treatment interruption" included to align with infusion page in the EDC system and "Subject" definition updated
- Protocol Summary: updated in alignment to the protocol sections updated
- Section 1.1: Including Oxbryta (voxelotor™) as approved by US FDA on 25-Nov-2019 for SCD treatment in adults and pediatric patients 12 years of age and older
- Section 1.1.2.1: Including first global approval for crizanlizumab obtained from the US FDA on 15-Nov-2019
- Table 2-1:
    - Clarifying that annualized rate of all VOCs leading to healthcare visit and treated at home is also part of efficacy objective over the entire study period
    - "Number of days with VOC" renamed to "duration of VOC leading to healthcare visit" as per definitions provided in Section 12.5.1 and in line with feedback received from scientific advice.
    - Secondary objective added: "To assess the annualized rate of VOCs managed at home in each group"
- Section 3:
    - Clarifying that HU/HC and/or L-glutamine medicinal products may be received by the subjects as standard of care only if approved by local HA
    - Sentences "Once eligibility criteria have been confirmed to Novartis via the eligibility checklist, the subject will be randomized and will receive investigational treatment" and "A subject eligibility checklist will be embedded into the IRT enrolment process" removed as not applicable per current process
    - Infusion time removed and reference to pharmacist manual made instead
- Section 5: Population description updated according to changes in Section 5.1
- Section 5.1
    - Revised inclusion criterion #4 to reflect that 1) prior VOC leading to healthcare visit must resolve at least 7 days prior to Week 1 Day 1 and 2) clarify that acute chest syndrome, priapism and hepatic or splenic sequestration are to be considered VOC in this study
    - Revised inclusion criterion #5 to 1) clarify that HU/HC and/or L-glutamine that may be received by the patients as standard of care must be medicinal products approved by local HA and must have been taken for at least 6 months and at a stable dose for at least 3 months and 2) clarify that, in case of HU/HC and/or L-glutamine intake, patients must have evidence of insufficient control of acute pain, such as at least one VOC leading to healthcare visit while on HU/HC or L-Glutamine treatment and 3) clarify that patients who have not been receiving any standard of care medication

(HU/HC, L-glutamine, and/or erythropoietin stimulating agent) must not have received it for at least 6 months prior to screening. The same changes have been implemented across the document when applicable
    - Revised inclusion criterion #6 to 1) clarify that central laboratory values used to determine patients eligibility must be met prior to Week 1 Day 1 visit and 2) include the possibility to use local laboratory values to confirm eligibility as per section 8.4.1
- Section 5.2
    - Revised exclusion criterion #12 to exclude hospitalizations within 7 days prior to Week 1 Day 1 dosing instead of prior to screening
    - Revised exclusion criterion #19 to remove resting QTcF parameter as crizanlizumab has no QT liability
    - Exclusion criterion #22 added to clarify that prior treatment with crizanlizumab or other selectin targeting agent and use of approved crizanlizumab is prohibited
- Section 6.1.1: modified as per updated Pharmacy Manual. Some information related to the study drug preparation, dispensation and timing has been removed. Reference to the Pharmacy Manual has been added
- Table 6-1: modified as per updated Pharmacy Manual
- Section 6.2.1:
    - Details for treatment with erythropoietin-stimulating agents to manage chronic symptomatic anemia added
    - Updated to reflect that EOS visit is not applicable to this study and it was replaced with the safety follow-up visit.
    - Updated to clarify that L-glutamine to be used as concomitant treatment has to be local HA approved medicinal product
    - Updated to clarify the concomitant use is permitted provided that the subject has been prescribed HU/HC or L-glutamine consistently over at least the 6 months and at a stable dose for at least 3 months prior to the screening visit
- Section 6.2.1.1: modified to clarify that the use of other forms of L-Glutamine not approved by local HA must be collected in the eCRF and to add instructions for crizanlizumab treatment in case a major surgery becomes necessary
- Section 6.2.2: clarifying that 1) prior treatment with crizanlizumab is not allowed as well as use of approved crizanlizumab during the entire study duration (both double-blind and open-label periods) and 2) new treatments to treat SCD and or to prevent/reduce VOCs are not permitted during the study except for those specifically mentioned in Sections 6.2.1 and 6.2.1.1
- Section 6.4: details about unblinding process in case of emergency situations has been added
- Table 6-2: Blinding levels and roles corrected as per current process
- Table 6-3:
    - Neutropenia (ANC) units updated to International System units
    - Criteria for body temperature in febrile neutropenia changed from ≥38.5 C to ≥ 38.3 C
    - Range for grade 1 to grade 4 isolated direct bilirubin has been clarified

  - Updated recommendation to continue study treatment for grade 1 infusion related reactions
  - For grade 3 infusion reaction, recommendation is updated from permanent discontinuation of study treatment to temporary interruption of study treatment
  - Foot note has been deleted regarding recommendation to continue study treatment at Investigator's discretion if total bilirubin > 3.0 × ULN is only due to indirect component
- Section 6.5.2.1:
  - Modified definition of potential DILI to include normal ALP along with elevation of transaminases and increase in TBIL
  - Criteria for subjects with normal ALT and Direct BIL value at baseline modified to include that the subjects should be without evidence of cholestasis
  - Text modified to reflect that LFTs will be repeated for certain defined criteria preferably within 48-72 hours
- Section 6.7: crizanlizumab and/or placebo solution preparation instructions updated to refer to the updated Pharmacy Manual
- Section 6.7.1.1: Information about the study drug accountability has been removed and reference to the Pharmacy Manual has been added
- Section 8: clarifying that a minimum of 21 days between 2 doses must be respected.
- Table 8-1
  - Treatment duration limited to week 259 for consistency with 4-week interval from week 15
  - Prior/concomitant medications assessments for anticoagulants, hydroxyurea/ hydroxycarbamide, L-glutamine and erythropoietin stimulating agent added for consistency with EDC system
  - Update to include that ECG shall not be performed on post dose week 1 day 1 and clarified to reflect that ECG will be performed on week 23, week 47 and then every 12 months
  - Clarifying that cardiac imaging can be performed before first dosing if not done within the last 12 weeks prior to start of study drug
  - Clarifying that pharmacogenetic samples can be collected at any time during the study. Note: The term 'pharmacogenomic' was updated to 'pharmacogenetic' across the document as more appropriate
  - Alcohol test and drug screen removed as crizanlizumab is not metabolized in the liver and drugs that are substrates, inhibitors or inducers of CYP450 are not expected to affect the PK of crizanlizumab
  - Optional TFQ assessment added as missed in previous Protocol version. Footnote #19 added to refer to Section 8.5.1
  - Headers for End of Treatment and Post-treatment follow-up Periods and respective visit names corrected for consistency with EDC system

  - Footnote #20 added to clarify that eligibility criteria listed in Section 8.6 must be met by subjects switching from placebo to crizanlizumab after completion of primary analysis
  - Footnote #21 added to inform that, for treatment visits following Week 1 Day 1 visit, patient's body weight at previous visit can be used to prepare the infusion in advanced in order to avoid delays in administering the investigational treatment. If more than 5% of difference between body weight at previous and current visits is identified, infusion will be re-prepared according to patient's body weight at the time of every particular visit.
  - Footnote #22 added to clarify type of VOCs to be collected as medical history of VOC
- Section 8.1: Updated per current IRT process in case of re-screening. For platelet count test, it has been clarified that local re-sampling is allowed at any time in case of clumping or other issues reported from the central laboratory.
- Section 8.1.1: "The investigator site will then register the subject in the IRT system to obtain the treatment number" has been removed as not applicable per current process
- Section 8.3.1
  - "Uncomplicated pain crisis" updated to "Uncomplicated VOC" for consistency
  - Resolution of an uncomplicated VOC has been clarified
  - Definition and/or duration of Acute Chest Syndrome, priapism, hepatic sequestration and splenic sequestration has been updated to add clarity.
  - Clarifying that visit to a medical facility for collection of analgesic prescription is allowed
  - Definition of VOC leading to healthcare visit and VOC managed at home have been updated
  - Definition of 'Other acute pain crises (APCs) managed at home' not meeting VOC conditions and of interest in the study has been clarified
  - Clarifying that subjects should contact the Investigator within 24 hours when they believe they are experiencing a VOC or other APC that they can manage at home.
  - Clarifying that VOCs/ other APCs occurring within 7 days following the documented resolution of a crisis event will be counted as part of the prior crisis.
- Section 8.4.1: Removal of alcohol test and drug screen from laboratory evaluations to be performed, allowance of local re-sampling at any time for platelet count test in case of clumping or other issues reported from the central laboratory and clarification of how to document the results of the local laboratory in the EDC system
- Table 8-4: Clarifying that glucose sample can be taken non-fasting. RBC morphology, blood alcohol screen and urine drug screen removed
- Clarifying that safety laboratory tests can be performed locally before dosing at the discretion of the investigator.
- Table 8-5:
  - ECG collection plan re-designed for clarity

  - ECG measures at Week 1 Day 1 (2h post dose) and at 105 days safety follow-up visit removed from collection plan
  - Clarifying that unscheduled ECG with clinically significant findings should be collected in triplicate and sent for central review
  - Footnote 'b' added to clarify time points for post dose ECG measures
- Section 8.4.2.1: parameters to be assessed by Echocardiogram are re-defined: PAP replaced with mPAP
- Section 8.5.1:
  - [redacted]
  - Information about the structure, completion and review of subject questionnaires has been added
  - Instructions to follow when entry in the diary has been missed are updated
  - [redacted]
  - Time points for TFQ collection have been added
  - Collection instructions for spontaneous information about AEs removed as not applicable.
- Table 8-6:
  - Clarifying that Follow up IG sample refers to last infusion + 105 days
  - Number of consecutive doses given to reach steady state sampling updated from 4 to 3
  - Foot note 'g' has been added to clarify when the 0.5 hr PK sample is to be collected

[redacted]

- Section 8-6: Clarifying that local laboratory re-sampling is allowed as described in section 8.4.1
- Section 9.1.1: "Unsatisfactory therapeutic event" and "Emergency unblinding before Primary Analysis, as described in section 6.6.2" added as reasons for discontinuation of study treatment
- Section 10.1.1: list of outcomes to be recorded in the eCRF updated to include recovering/resolving AEs
- Section 12.1: Conditions for evaluable PK profile in the definition of PAS1 corrected per consistency with updated Table 8-6. The term "Primary" for PK parameter removed as not applicable per analysis planned.
- Section 12.3: "permanent discontinuation" removed as not collected in the CRF
- Section 12.4.2: definition of the treatment effect of interest for prohibited medications clarified in line with section 6.2.2
- Section 12.4.4:

  - definition of the treatment effect of interest for prohibited medications clarified in line with section 6.2.2.
  - definition of the age subgroup changed considering number of subjects ≥ 65 years expected to be low
- Section 12.5: changes made for consistency with updated Objectives section
- Section 12.5.1: Details for closure principle provided for clarity. Other changes made for consistency with updated Objectives section and to clarify that in the analysis, VOC leading to healthcare visit referred to VOC assessed by Adjudication Committee and VOC managed at home referred to VOC reported in the CRF.
- Section 12.5.3: Individual plots of concentration-time profile and pre-dose concentrations removed considering the high number of subjects. Geometric mean replaced by median in the concentration.-time profiles over time and pre-dose concentrations over time plots given the distribution of the PK observations
- Section 12.5.4: Individual plots of PD-time profile removed considering the high number of subjects and geometric mean replaced by median in the PD-time profiles over time plots given the distribution of the PD observations
- Section 15: Oxbryta-USPI (2019) reference was added

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Protocol summary

Protocol number	CSEG101A2301
Title	A Phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab versus placebo, with or without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients with Vaso-Occlusive Crises (STAND)
Brief title	Study of two doses of crizanlizumab versus placebo in adolescent and adult sickle cell disease patients
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Pre-clinical data have established P-selectin as a key mediator of vaso-occlusion in SCD and suggest that its blockade could eliminate or reduce VOCs. The A2201 study (SUSTAIN) compared the mean trough percentage P-selectin inhibition obtained with crizanlizumab following administration of 2.5 mg/kg dose and 5.0 mg/kg dose and suggested that the degree of clinical benefit may be correlated with achieving a certain level of P-selectin inhibition. Since trough concentration is highly correlated with % P-selectin inhibition, 7.5 mg/kg is the proposed dose to achieve higher % P-selectin inhibition in SCD patients. The purpose of this study is to compare the efficacy and safety of 2 doses of crizanlizumab (5.0 mg/kg and 7.5 mg/kg) versus placebo in adolescent and adult SCD patients with history of VOC leading to healthcare visit.
Primary Objective(s) and Key Secondary Objective(s)	Primary Objective: • To compare the efficacy of 7.5 mg/kg of crizanlizumab versus placebo on the annualized rate of VOC leading to healthcare visit, in addition to standard of care • To compare the efficacy of 5.0 mg/kg of crizanlizumab versus placebo on the annualized rate of VOC leading to healthcare visit, in addition to standard of care Key Secondary Objective: • To compare the efficacy of 7.5 mg/kg versus placebo on the annualized rate of all VOCs (managed at home + leading to healthcare visit) • To compare the efficacy of 5.0 mg/kg versus placebo on the annualized rate of all VOCs (managed at home + leading to healthcare visit)
Secondary Objective(s)	• To assess the annualized rate of VOCs managed at home in each group • To assess the time to first and second VOC leading to healthcare visit in each group • To assess rate of participants free from VOC leading to healthcare visit in each group • To assess the duration of VOC leading to healthcare visit in each group • Healthcare resource utilization (visits to clinic, Emergency room (ER) and hospitalizations) in each group • To assess SCD-related renal damage in each group • To characterize the pharmacokinetic (PK) profile of crizanlizumab at 5.0 and 7.5 mg/kg • To characterize the pharmacodynamic (PD) (P-selectin inhibition) of crizanlizumab at 5.0 and 7.5 mg/kg • To assess efficacy, safety and immunogenicity of crizanlizumab over the study period (taking into account potential treatment switch after primary analysis)
Study Design	Phase 3, randomized, placebo-controlled, double-blind study comparing 2 doses of crizanlizumab (5.0 mg/kg and 7.5 mg/kg) versus placebo in addition to standard of

	care that patients might be taking at the time of study start in adolescent and adult SCD patients with history of VOC leading to healthcare visit. 240 participants will be randomized in a 1:1:1 ratio to either 5.0 mg/kg or 7.5 mg/kg of crizanlizumab or placebo. Central randomization will be stratified by concomitant HU/HC usage (yes/no) and baseline rate of VOCs leading to healthcare visit in 12 months prior to Screening (2 to 4 vs ≥ 5 VOCs). Following conduct of the primary analysis (once all randomized participants have reached 1 year of investigational treatment or discontinued within year 1), unblinding and change to an alternative dose or switch to crizanlizumab will be permitted for each individual participant, based on primary study results and investigator's assessment of sub-optimal efficacy vs. apparent therapy-related toxicity. Participants will receive open label investigational drug for the remaining period of treatment. It is planned to observe participants for five years on investigational treatment; earlier termination of the study can be considered.
Study Population	SCD patients aged 12 years and older (including at least 48 adolescents) who experienced at least 2 VOCs leading to healthcare visit in the 12 months prior to screening visit, and who are not planning to initiate HU/HC or L-glutamine (local HA approved medicinal product) during the first year of investigational treatment. Patients who have been taking HU/HC or L-glutamine for at least 6 months and a stable dose for at least 3 months and plan to continue taking at the same dose and schedule until the patient has reached one year of investigational treatment will be permitted.
Key Inclusion criteria	1. Written informed consent must be obtained prior to any screening procedures 2. Male or female patients aged 12 years and older on the day of signing informed consent. Adolescents include patients aged 12 to 17 years old and adults ≥ 18 years 3. Confirmed diagnosis of SCD by Hb electrophoresis or high performance liquid chromatography (HPLC) (performed locally). All SCD genotypes are eligible, genotyping is not required for study entry. 4. Experienced at least 2 VOCs leading to healthcare visit within the 12 months prior to screening visit as determined by medical history. Prior VOC leading to healthcare visit must resolve at least 7 days prior to Week 1 Day 1 and must include: a. Pain crisis defined as an acute onset of pain for which there is no other medically determined explanation other than vaso – occlusion (refer to Section 8.3.1 for details on VOC definition), b. which requires a visit to a medical facility and/or healthcare professional c. and receipt of oral/parenteral opioids or parenteral nonsteroidal anti-inflammatory drug (NSAID) analgesics Acute chest syndrome (ACS), priapism and hepatic or splenic sequestration will be considered VOC in this study. 5. If receiving HU/HC or L-glutamine (local HA approved medicinal product), must have been receiving the drug for at least 6 months and at stable dose for at least 3 months prior to Screening visit and plan to continue taking it at the same dose and schedule until the participant has reached one year of study treatment. Patients must have evidence of insufficient control of acute pain, such as at least one VOC leading to healthcare visit while on HU/HC or L-Glutamine treatment. If receiving erythropoietin stimulating agent must have been receiving the drug for at least 6 months prior to screening visit and plan to continue taking the drug to maintain stable Hb levels at least until the participant has reached one year of study treatment Patients who have not been receiving any of these drugs (HU/HC, L-glutamine, and/or erythropoietin stimulating agent) must not have received it for at least 6 months prior to screening.

	6. Patients must meet the following central laboratory values prior to Week1 Day 1. In case of re-sampling needed, local laboratory values are allowed. Refer to Section 8.4.1 for further details • Absolute Neutrophil Count ≥1.0 x 10^9/L • Platelet count ≥75 x 10^9/L • Hemoglobin: for adults (Hb) ≥4.0 g/dL and for adolescents (Hb) ≥5.5 g/dL • Glomerular filtration rate ≥ 45 mL/min/1.73 m^2 using CKD-EPI formula in adults, and Schwartz formula in adolescents • Direct (conjugated) bilirubin < 2.0 x ULN • Alanine transaminase (ALT) < 3.0 x ULN 7. ECOG performance status ≤ 2.0 for adults and Karnofsky ≥ 50% for adolescents
Key Exclusion criteria	1. History of stem cell transplant. 2. Participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) and/or planning on undergoing an exchange transfusion during the duration of the study; episodic transfusion in response to worsened anemia or VOC is permitted. 3. Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation. History of severe hypersensitivity reaction to other monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction. 4. Received active treatment on another investigational trial within 30 days (or 5 half-lives of that agent, whichever is greater) prior to Screening visit or plans to participate in another investigational drug trial. 5. 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. 6. Concurrent severe and/or uncontrolled medical conditions which, in the opinion of the Investigator, could cause unacceptable safety risks or compromise participation in the study. 7. History or current diagnosis of ECG abnormalities indicating significant risk of safety such as: • Concomitant clinically significant cardiac arrhythmias (e.g ventricular tachycardia), and clinically significant second or third degree AV block without a pacemaker • History of familial long QT syndrome or know family history of Torsades de Pointes 8. Not able to understand and to comply with study instructions and requirements. 9. Received prior treatment with crizanlizumab or other selectin targeting agent.
Study treatment	Crizanlizumab (SEG101) at 5.0 mg/kg Crizanlizumab (SEG101) at 7.5 mg/kg Placebo
Efficacy assessments	• VOC events leading to healthcare visit • VOC events managed at home • Hospitalizations, clinic and ER visits (both overall and VOC-related) • Albuminuria and albumin creatinine ratio (ACR) • [redacted] • Echocardiograph • Other acute pain crises (APCs)
Key safety assessments	• Monitoring of AEs/SAEs • Vital signs

	• Hematology, chemistry, coagulation and urinalysis • Growth and sexual maturity assessment in adolescents (Tanner stage) • ECGs at relevant time points • Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab
Other assessments	• PK parameters • PD parameter (%P-selectin inhibition) [redacted] • Pharmacogenetic
Data analysis	The primary efficacy endpoint, annualized rate of VOC leading to healthcare visit over the first year post-randomization, will be analyzed based on the data from the Full Analysis Set (FAS) according to the treatment arm and the stratification factors participants were randomized to. A negative binomial regression model with treatment and randomization stratification factors as covariates will be used for analysis, with the logarithm of observation time as offset. The hypotheses will be tested using the Wald test statistic within the generalized linear model assuming a negative binomial distribution. The estimates of annualized VOC rates between treatment groups and their 95% confidence intervals will be provided. The key secondary endpoint, the annualized rate of all VOCs leading to healthcare visit and treated at home over the first year post randomization, will be analyzed using the same method used in the primary endpoint. To control the overall family-wise type I error rate (FWER) an appropriate multiplicity adjustment procedure using a closed testing strategy will be applied to the analyses of the primary and key secondary endpoints for the 2 doses comparisons to placebo. The key secondary endpoint of a given dose will be tested only if the difference in the primary endpoint for the same dose is statistically significant. The primary analysis will be conducted once all randomized participants have reached one year of investigational treatment or discontinued within year 1.
Key words	Sickle cell disease, crizanlizumab, adolescents, vaso-occlusive crisis, adults

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

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

SCD is the most common single gene disorder in African Americans, affecting approximately 1 in 375-600 people of African ancestry Nietert et al 2002. Sickle cell conditions are also common among people of Mediterranean countries, Africa, Middle East, India, Caribbean and parts of South and Central America. The most frequent and typically most severe form is homozygous HbSS (sickle cell anemia) ($\alpha_2 \beta s2$, HbS). Other forms of sickle cell disease include compound heterozygous conditions, such as hemoglobin C (HbC) with HbS (HbSC), HbS with β-thalassemia (HbS/β^0-thalassemia or HbS/β^+-thalassemia), and HbS with other variants Ware et al 2017. Clinical signs appear within the first 6 months of life, but there is considerable variability in severity Gill et al 1995 resulting from genetic and environmental factors. Patients describe acute pain crises and chronic pain clearly as the most debilitating effects on their lives, affecting them physically and emotionally. Fatigue and cognitive effects also emerge as other debilitating effects. In addition, organ-damage and long-term complications have also a severe effect on them. As a result of these complications, patients often have reduced quality of life (QoL), significant anxiety, depression, and short-life expectancy Kanter and Kruse-Jarres 2013.

Current treatment:

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

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

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

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

L-glutamine (Endari™) is approved in the United States to reduce the acute complications of SCD in adult and pediatric patients 5 years and older and Oxbryta (voxelotor™) has been approved by FDA since 25 Nov 2019 for the treatment of sickle cell disease (SCD) in adult and pediatric patients 12 years of age and older.

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

1.1.1.1 Role of P-selectin in VOC

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

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

1.1.2 Introduction to investigational treatment

1.1.2.1 Overview of crizanlizumab (SEG101)

Crizanlizumab is a selective humanized monoclonal antibody (mAb) that binds to P-selectin with high affinity, blocking its interaction with its ligands, including PSGL-1. Extensive pre-clinical data have established P-selectin as a key mediator of VOC in SCD Matsui et al 2001 and suggest that its blockade could eliminate or reduce VOC.

The compound was previously developed by Reprixys Pharmaceuticals Corporation under the investigational drug code SelG1. Novartis acquired the company on 18-Nov-2016, and is now the drug developer and sponsor for crizanlizumab, under the investigational drug code, SEG101. Crizanlizumab was first approved in the US on 15-Nov-2019 and is now approved in more than 40 countries for the prevention/reduction of VOCs in adults and pediatric patients

aged 16 years and older with SCD.. The crizanlizumab IB provides detailed information related to toxicology, nonclinical pharmacology, drug properties and preclinical data.

1.1.2.2 Clinical experience

Phase I Clinical Study (Reprixys study code: [Se1G1-00003]; Novartis study code: [CSEG101A2101])

Throughout this description of CSEG101A2101, the study drug is denoted as crizanlizumab and refers to SelG1.

The objectives of this study were to evaluate the safety, PK, PD, and immunogenicity of IV administered crizanlizumab versus placebo in 27 healthy participants at ascending dose levels (0.2, 0.5, 1.0, 5.0 mg/kg and 8.0 mg/kg).

At this dose levels, mean half-life ($T_{1/2}$) values increased in a dose-dependent manner.

The exposure to crizanlizumab (mean Cmax, AUC0-t, and AUC0-∞) increased in a greater than proportional manner over the dose range of 0.2 to 8.0 mg/kg. For participants 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 indicated that no specific antibody (Ab) response to crizanlizumab occurred in any participants receiving up to 2 doses of crizanlizumab.

Phase II Clinical Study (SUSTAIN study; Reprixys study code: [Se1G1-00005]; Novartis study code: [CSEG101A2201])

Throughout this description of SUSTAIN, the study drug is denoted as crizanlizumab and refers to SelG1.

The objective of this pivotal, randomized, placebo-controlled study was to assess the safety and efficacy of crizanlizumab with or without HU/HC therapy in SCD patients with a history of VOC leading to a healthcare visit. A total of 198 SCD patients aged 16-65 years (inclusive), with any SCD genotype, a history of crisis within the previous 12 months, and either with a steady dose of HU/HC or not taking HU/HC, were randomized 1:1:1 to crizanlizumab 5.0 mg/kg, crizanlizumab 2.5 mg/kg or placebo.

The median annual rate of VOC leading to a healthcare visit was 45.3% lower with 5 mg/kg crizanlizumab than with placebo (Hodges-Lehmann, median absolute difference of -1.01 versus placebo, 95% confidence interval (CI) [-2.00, 0.00]). The difference between the 5 mg/kg arm and placebo arm was statistically significant (Wilcoxon rank sum test, p= 0.010). The median annual rate of uncomplicated crises and median number of days hospitalized, were 62.9% and 41.8% lower in the 5.0 mg/kg than in the placebo group, respectively. Crizanlizumab also delayed the time to onset of first and second VOC, and consistent benefit was further observed in a number of clinically relevant subgroups for the primary endpoint.

Crizanlizumab was generally well tolerated with similar incidence of treatment-emergent adverse events (TEAEs) across the three groups, and overall low incidence of discontinuations

due to TEAEs (<5%). The proportion of participants experiencing SAEs was 25.8% at 5.0 mg/kg, 32.8% at 2.5 mg/kg and 27.4% in the placebo group. 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 none was deemed to be treatment-related. Please refer to IB for further information.

Overall, treatment of SCD patients with crizanlizumab at 5.0 mg/kg showed positive clinical activity as demonstrated by a statistically significant and clinically relevant decrease in the annual VOC rate compared with placebo and it was also found to be well tolerated.

All completed clinical studies described above were performed by Reprixys Pharmaceuticals Corporation. These studies were conducted using monoclonal antibodies produced in Invitrogen CHO-S cells (SelG1). To ensure supply of future clinical studies as well as commercial demand, Novartis has optimized the production of crizanlizumab. SEG101 will be used in future clinical/toxicological studies and as a commercial product.

Phase I Clinical Study (Novartis study code: [CSEG101A2102])

The primary objective of this study was to evaluate the PK and PD (% P-selectin inhibition) comparability of crizanlizumab (SEG101 (test) and SelG1 (reference)) following a single IV infusion of 5.0 mg/kg in 61 healthy participants. This study also included an exploratory analysis with 7 healthy participants treated at 7.5 mg/kg of SEG101, in order to characterize its PK and PD at a higher dose for potential assessment in future studies. Comparable Cmax and PD were observed between SEG101 and SelG1. The areas under the curve (AUCinf and AUClast) for SEG101 were 28% greater than SelG1, and the half-lives were similar with parallel concentrations-time profiles and the difference in AUC is not expected to affect the efficacy. Crizanlizumab PK with SEG101 exhibited less variability as compared to SelG1. Treatment with SEG101 and SelG1 was safe (i.e., no death and grade 3/4 AEs) and well tolerated with a similar safety profile. SEG101 at 7.5 mg/kg showed no apparent safety concern with 62% greater AUC (AUCinf) than 5.0 mg/kg.

Phase II Clinical Study (Novartis study code: [CSEG101A2202])

A Phase 2, multicenter, open-label Study in adolescent and adult SCD patients with VOC leading to healthcare visit is ongoing to characterize PK and PD (P-selectin inhibition) of crizanlizumab at 5.0 mg/kg. This study also includes an exploratory cohort to characterize PK and PD of crizanlizumab at 7.5 mg/kg.

Phase II Clinical Study (Novartis study code: [CSEG101B2201]) - Pediatric study

A Phase 2, multicenter, open-label study to confirm and establish appropriate dosing, and to evaluate the PK and safety of crizanlizumab, with or without HU/HC in pediatric SCD patients (6 months <18 years old) with a history of at least one VOC leading to healthcare visit in the prior 12 months is ongoing. Three groups will be sequentially enrolled with PK/PD and safety assessments: 12 to <18 years, 6 to <12 years, and 2 to <6 years. Once the appropriate dose is confirmed in participants aged 2 to <6 years, participants aged 6 to <24 months can be enrolled.

1.2 Purpose

The purpose of this study is to compare the efficacy and safety of 2 doses of crizanlizumab (5.0 mg/kg and 7.5 mg/kg) versus placebo in adolescent and adult SCD patients with history of VOC leading to healthcare visit.

1.2.1 Study rationale and purpose

Extensive pre-clinical data have established P-selectin as a key mediator of vaso-occlusion in SCD and suggest that its blockade could eliminate or reduce VOCs Matsui et al 2001.

In the SUSTAIN study, the mean trough percentage P-selectin inhibition obtained with crizanlizumab at 4 weeks post-dose (from Week 6 to Week 50) ranged from 24% to 40% following administration of 2.5 mg/kg dose and from 64% to 76% following administration of 5.0 mg/kg dose, which suggests that the degree of clinical benefit may be correlated with achieving a certain level of P-selectin inhibition.

Adolescents and adults with SCD share the same etiology, genetic variability and pathophysiology, causing a comparable range of clinical manifestations and prognostic factors and lead to a similar treatment approach for the disease. Like adults, adolescents experience both acute and chronic pain, and the prevalence of complications, such as pulmonary hypertension and kidney dysfunction, begin to increase at this age compared to younger ages. The rate of VOCs is similar to adults (20% of adolescents experience 1-3 VOCs per year compared to 21% in adults aged 30-39 years old) Platt et al 1991. In addition, adolescents and young adults have the highest rates of hospitalizations, partially attributable to the progress of the disease and often turbulent transition from pediatric to adult care. Based on the above, the benefits and risks of crizanlizumab in adolescents are expected to be similar to the adult population.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To compare the efficacy of 7.5 mg/kg of crizanlizumab versus placebo on the annualized rate of VOC leading to healthcare visit, in addition to standard of care • To compare the efficacy of 5.0 mg/kg of crizanlizumab versus placebo on the annualized rate of VOC leading to healthcare visit, in addition to standard of care	• Annualized rate of VOC events leading to healthcare visit in each treatment group over the first year post-randomization
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Key secondary objective:** To compare the efficacy of 7.5 mg/kg versus placebo on the	• Annualized rate of all VOCs leading to healthcare visit and treated at home (based on documentation

Objective(s)	Endpoint(s)
annualized rate of all VOCs (managed at home + leading to healthcare visit) To compare the efficacy of 5.0 mg/kg versus placebo on the annualized rate of all VOCs (managed at home + leading to healthcare visit)	by health care provider following contact with participant) over the first year post randomization
• To assess the annualized rate of VOCs managed at home in each group	• Annualized rate of VOCs managed at home over the first year post randomization
• To assess the duration of VOCs leading to healthcare visit in each group	• Duration of VOCs leading to healthcare visit over the first year post randomization
• To assess rate of participants free from VOC leading to healthcare visit in each group	• Number and percentage of participants free from VOCs leading to healthcare visit in each group over the first year post randomization
• To assess the time to first and second VOC leading to healthcare visit in each group	• The time to first and second VOC calculated respectively as the time from date of randomization until the first and the second VOC leading to healthcare visit over the first year post randomization
• Healthcare resource utilization (visits to clinic, Emergency room (ER) and hospitalizations) in each group versus placebo	• Annualized rate of visits to clinic, Emergency room (ER) and hospitalizations, both overall and VOC-related over the first year post randomization
• To assess SCD-related renal damage in each group	• Evolution of albuminuria and ACR over the first year post randomization
• To characterize the pharmacokinetic (PK) profile of crizanlizumab at 5.0 and 7.5 mg/kg	• PK parameters after the first and fifth dose (e.g., AUC, Cmax, Tmax, half-life)
• To characterize the pharmacodynamic (PD) (P-selectin inhibition) of crizanlizumab at 5.0 and 7.5 mg/kg	• PD parameter (P-selectin inhibition) after the first and fifth dose
• To assess efficacy, safety and immunogenicity of crizanlizumab over the study period (taking into account potential treatment switch after primary analysis)	• Annualized rate of VOCs leading to healthcare visit • Annualized rate of all VOCs leading to healthcare visit and treated at home • Annualized rate of VOCs managed at home • Number, seriousness, severity, and causality assessments of treatment-emergent adverse events, including infections (serious, non-serious and opportunistic infections) and other safety data as considered appropriate • Absolute change from baseline in hemoglobin • Growth and sexual maturity assessment in adolescents (Tanner stage) • Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab
[redacted]	

3 Study design

This is a multicenter, randomized, double-blinded, parallel-group Phase 3 study in which two doses of crizanlizumab, 5.0 mg/kg and 7.5 mg/kg, will be compared to placebo in addition to standard of care in adolescent and adult SCD patients with history of VOC leading to healthcare visit.

The study will include participants aged 12 years and older with confirmed diagnosis of SCD (all genotypes are eligible) who have experienced at least 2 VOCs leading to healthcare visit in the 12 months prior to screening visit. Participants may receive HU/HC and/or L-glutamine (local HA approved medicinal product) as a standard of care, as indicated in Section 6.2.1.

240 participants, including a minimum of 48 adolescents, will be randomized in a 1:1:1 ratio to either 5.0 mg/kg or 7.5 mg/kg of crizanlizumab or placebo. Central randomization will be stratified by concomitant HU/HC usage (yes/no) and baseline rate of VOCs leading to healthcare visit in 12 months prior to screening visit (2-4 vs $\geq$ 5 VOCs). In order to allow adequate opportunity for enrollment into each of the four strata (the four possible combinations of the stratification factors), a capping of 90 adult participants per stratum will be implemented.

Following randomization, participants will receive their first dose of investigational treatment (crizanlizumab or placebo) via IV administration on Week 1 Day 1, followed by a second dose 14 days later (Week 3 Day 1), and then investigational treatment administration will take place every 4 weeks for a total on-study treatment period of up to 5 years. Following conduct of the primary analysis, once all randomized participants have reached one year of investigational treatment or discontinued within year one, unblinding and change from placebo to crizanlizumab or to an alternative dose of crizanlizumab will be permitted for each individual participant. See Section 6.1.5.2 for further information. It is planned to observe participants for 5 years on investigational treatment, however early termination of the study could be considered. Participants will continue on study until 105 days after discontinuing drug or until receiving crizanlizumab commercially or through a different study or drug access program. The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete the post-treatment follow-up.

Screening

Within 28 days before randomization, written informed consent, according to local guidelines, will be signed by the participants and prior to any study related screening procedures are performed. All screening evaluations must be performed during the screening period from day -28 to day -1.

Treatment

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

Participants will receive investigational treatment by IV infusion on Week 1 Day 1, Week 3 Day 1, and then on Day 1 of every 4-week cycle. Refer to the Pharmacy Manual for instructions on preparation and dispensation of the investigational treatment.

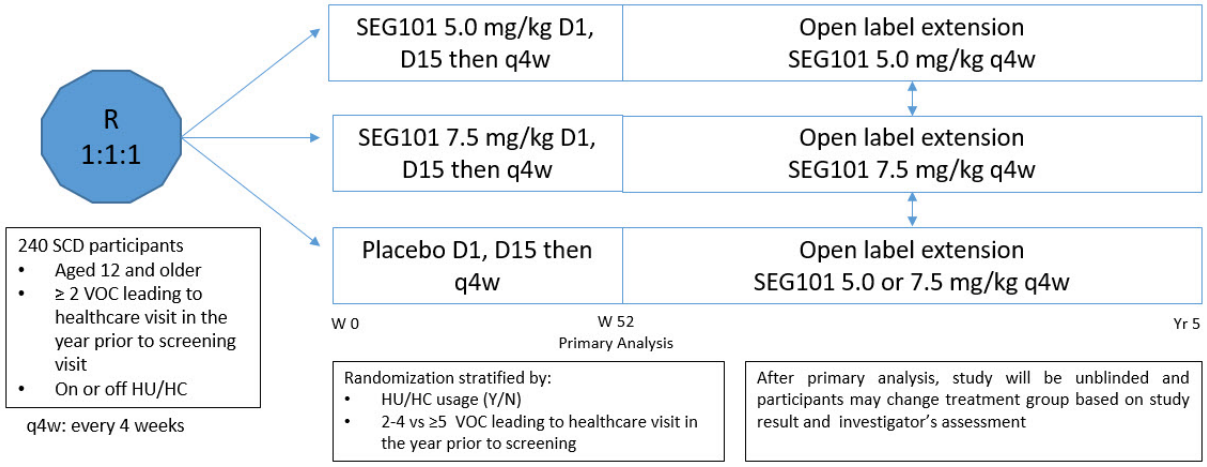
Safety will be monitored as outlined in Section 8.4. Participants will receive investigational treatment for 5 years or until unacceptable toxicity, death, are lost to follow-up or discontinued from the investigational treatment for any other reasons at the discretion of the investigator or the participant.

Following the treatment discontinuation, participants will perform an End of Treatment visit.

Post-treatment follow-up

All participants will remain in the study until completion of the 105 day safety follow-up visit, except the participants continuing crizanlizumab via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment) upon completion of their EOT visit.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

This placebo-controlled randomized double-blind study is designed to confirm efficacy and safety of crizanlizumab 5mg/kg dose and assess safety and efficacy of a higher dose (7.5mg/kg).

4.2 Rationale for dose/regimen and duration of treatment

The doses chosen for the SUSTAIN study (see Section 1.1.2.2 for further details) were based on P-selectin inhibition of SelG1 evaluated in healthy participants, as well as the acceptable safety experience observed in the Phase I study [CSEG101A2101]. The Phase I study [CSEG101A2101] showed that a single dose of SelG1 at 5.0 mg/kg and two doses of 8.0 mg/kg at a 2-week interval, respectively, maintained complete (100%) P-selectin inhibition at least for 28 days. Subsequently, in another Phase I study [CSEG101A2102] with healthy participants, the PD comparability between SEG101 and SelG1 was demonstrated with complete P-selectin inhibition, while the SEG101 exposure (Cmax and AUC) was greater at 7.5 mg/kg than 5 mg/kg with similar safety profiles. The Phase II study with SCD participants, or SUSTAIN study showed dose-dependent P-selectin inhibition and efficacy at the doses of 2.5 mg/kg and 5.0 mg/kg of crizanlizumab, indicating that a dose higher than 5.0 mg/kg may potentially achieve greater P-selectin inhibition and/or efficacy in SCD participants. Adult and pediatric SCD patients are known to have the similar soluble P-selectin concentration at the identified range (42.5 to 268 ng/mL in adult patients (Kanavaki 2012, Blann 2008, Al Najjar et al Najjaret 2017); 29.7 to 370 ng/mL in pediatric patients (Hatzipantelis 2013, Colombatti 2013, Krishnan 2010, Setty 2012). Therefore, crizanlizumab at the dose of 7.5 mg/kg may potentially lead to greater P-selectin inhibition and/or efficacy in SCD patients.

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

This study will compare 2 doses of crizanlizumab versus placebo: 5.0 mg/kg which has shown efficacy in reducing the number of VOCs in SCD patients at the age of 16 years and over, and a higher dose (7.5 mg/kg). The placebo will be used as a comparator to provide objective

evidence of clinical efficacy, and safety data generated from participants exposed to the experimental drug.

Participants will continue on standard of care, including HU/HC and/or L-glutamine, as established prior to study entry, thereby justifying potential treatment for placebo. Please refer to Section 6.2.1 for details.

4.4 Purpose and timing of interim analyses/design adaptations

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

4.5 Risks and benefits

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

Pooled safety data from the SUSTAIN and CSEG101A2202 studies in patients treated with crizanlizumab 5 mg/kg (n=111 patients, 31-Mar-2019 cutoff) showed that crizanlizumab is generally associated with a favorable safety profile. Adverse drug reactions (ADRs) were nausea (16.2%), back pain (15.3%), arthralgia (14.4%), pyrexia (14.4%), abdominal pain (9.0%), diarrhea (8.1%), pruritus (7.2%), vomiting (5.4%), myalgia (4.5%), musculoskeletal chest pain (4.5%), oropharyngeal pain (3.6%), infusion site reaction (2.7%), and infusion-related reaction (1.8%).

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

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

Infusion-related reactions (IRRs)

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

Additionally, a broad search for IRRs using an extensive list of potential signs and symptoms related to infusion reactions, and occurring within 24 hours of the infusion, identified 28.8% of patients in the safety pool with at least one event. Most of these events were reported in 1 or 2 patients only, except for nausea (9.0%), headache (8.1%), arthralgia and back pain (4.5%), and

fatigue and myalgia (2.7%). In the SUSTAIN study, IRRs using this broader search were more frequent in the 5 mg/kg arm (34.8%) compared to the placebo arm (21.0%). However, except for nausea, none of the events were reported with an absolute differences of more than 5% in the crizanlizumab 5 mg/kg vs. the placebo arm. In summary, current data suggest that administration of crizanlizumab can be associated with IRRs, including pain events, some of which can be severe and/or require hospitalization.

Immunogenicity

Administration of mAb can be associated with immunogenicity, including development of anti-drug antibodies (ADA) or hypersensitivity following treatment with crizanlizumab). In clinical studies, treatment-emergent ADAs were transiently detected in 1 patient among the 111 patients who received crizanlizumab 5 mg/kg (0.9%). There was no evidence of an altered PK/PD or safety profile with ADA development.

Infections

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

Infection-related AEs (based on all preferred terms included in the system organ class "Infections") were reported in 43.2% patients in the safety pool. The most frequently reported infections were urinary tract infection (9.9%), upper respiratory tract infections (8.1%), pneumonia and sinusitis (4 patients each, 3.6%). Most infections were low in severity (grade 1 or 2). In the randomized SUSTAIN study, infection-related AEs was similar across the arms: 53.0% in the crizanlizumab 5 mg/kg and 53.2% in the placebo arm. In addition, there was no difference between the arms in the incidence of neutropenia or white blood cell counts.

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

Effect on hemostasis

Considering the mode of action of crizanlizumab and physiological role of P-selectin, a potential effect on the hemostatic system was evaluated by searching for AEs related to hemorrhage, abnormal laboratory parameters. In the safety pool, a search for hemorrhagic events identified 13 (11.7%) patients, mostly related to abnormal laboratory findings. Except for prolonged prothrombin time (PT) reported in 3 (2.7%) patients, these events were reported in 1 or 2 patients only. None were grade 4 or led to study withdrawal, and none were considered treatment related as per investigator assessment. The only grade 3 event was decreased hemoglobin, consistent with hemolysis and the underlying disease.

In SUSTAIN study, hemorrhagic events were reported in 11 (16.7%) patients in the 5 mg/kg and 8 (12.9%) patients in the placebo arm, mostly related to laboratory abnormalities. Of note, 1 event (intracranial hemorrhage) reported in the 2.5 mg/kg arm was considered serious

(grade 4, hospitalization) and led to study drug discontinuation. Cerebrovascular accidents, including hemorrhagic stroke, are known complication and leading cause of death in patients with SCD.

In summary, bleeding events were rare, with the majority of the observed AEs being abnormal laboratory parameters on single occasions. The available data do not suggest an adverse effect of crizanlizumab on hemostasis.

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

Laboratory test interference with automated platelet counts

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

QT prolongation and hepatic safety

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

Pregnancy and lactation

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

Appropriate eligibility criteria and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.2.1.1. The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures and close clinical monitoring. If deemed clinically necessary, participants optionally could be kept in-the hospital for 24 hours following an investigational treatment dose.

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

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

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

SCD patients aged 12 years and older (including a minimum of 48 adolescents) who experienced at least 2 VOCs leading to healthcare visit in the 12 months prior to screening visit, and who are not planning to initiate HU/HC or L-glutamine during the first year of investigational treatment. Patients who have been taking HU/HC or L-glutamine (local HA approved medicinal product) for at least 6 months at a stable dose for at least 3 months and plan to continue taking at the same dose and schedule until the participant has reached one year of investigational treatment will be permitted. Participants must have evidence of insufficient control of acute pain, such as at least one VOC leading to healthcare visit while on HU/HC or L-Glutamine treatment. See Section 6.2.1 Concomitant therapy for further details. A capping of 90 adult participants per stratum will be implemented (Section 3).

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

5.1 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures
2. Male or female patients aged 12 years and older on the day of signing informed consent. Adolescent include patients aged 12 to 17 years old and adults ≥ 18 years
3. Confirmed diagnosis of SCD by hemoglobin electrophoresis or high performance liquid chromatography (HPLC) [performed locally]. All SCD genotypes are eligible, genotyping is not required for study entry

4a. Experienced at least 2 VOCs leading to healthcare visit within the 12 months prior to screening visit as determined by medical history. Prior VOC leading to healthcare visit must resolve at least 7 days prior to Week 1 Day 1 and must include:

   a. Pain crisis defined as an acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion (refer to Section 8.3.1 for details on VOC definition)
   b. which requires a visit to a medical facility and/or healthcare professional
   c. and receipt of oral/parenteral opioids or parenteral nonsteroidal anti-inflammatory drug (NSAID) analgesics

   Acute chest syndrome (ACS), priapism and hepatic or splenic sequestration will be considered VOC in this study (refer to Section 8.3.1 for further definition).

5. If receiving HU/HC or L-glutamine (local HA approved medicinal product), must have been receiving the drug for at least 6 months and at a stable dose for at least 3 months

prior to Screening visit and plan to continue taking it at the same dose and schedule until the participant has reached one year of study treatment. Patients who have not been receiving such drug must not have received it for at least 6 months prior to Screening visit to be included. Patients must have evidence of insufficient control of acute pain, such as at least one VOC leading to healthcare visit while on HU/HC or L-Glutamine treatment. If receiving erythropoietin stimulating agent, must have been receiving the drug for at least 6 months prior to Screening visit and plan to continue taking the treatment to maintain stable Hb levels at least until the participant has reached one year of study treatment. See Section 6.2.1 Concomitant therapy for further details.

Patients who have not been receiving HU/HC, L-glutamine, and/or erythropoietin stimulating agent must not have received it for at least 6 months prior to screening visit.

6. Patients must meet the following central laboratory values prior to Week 1 Day 1. In case of re-sampling needed, local laboratory values are allowed. Refer to Section 8.4.1 for further details:
   - Absolute Neutrophil Count $\geq 1.0 \times 10^9$/L
   - Platelet count $\geq 75 \times 10^9$/L
   - Hemoglobin: for adults (Hb) ≥ 4.0 g/dL and for adolescents (Hb) ≥ 5.5 g/dL
   - Glomerular filtration rate ≥ 45 mL/min/1.73 m^2 using CKD-EPI formula in adults, and Shwartz formula in adolescents
   - Direct (conjugated) bilirubin $< 2.0 \times$ ULN
   - Alanine transaminase (ALT) $< 3.0 \times$ ULN
7. ECOG performance status ≤ 2.0 for adults and Karnofsky $\geq 50\%$ for adolescents
8. Received standard age-appropriate care for SCD, including an up-to-date record of immunizations, as per local requirements

5.2 Exclusion criteria

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

1. History of stem cell transplant
2. Received blood products within 30 days prior to Week 1 Day 1 dosing
3. Participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) and/or planning on undergoing an exchange transfusion and/or plasmapheresis during the duration of the study; episodic transfusion in response to worsened anemia or VOC is permitted
4. Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation. History of severe hypersensitivity reaction to other monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction
5. Use of therapeutic anticoagulation or antiplatelet therapy (other than aspirin or NSAIDs) within the 10 days prior to Week 1 Day 1 dosing. Note: Prophylactic anticoagulant dose is permitted, as per local guidelines

6. Received active treatment on another investigational trial within 30 days (or 5 half-lives of that agent, whichever is greater) prior to Screening visit or plans to participate in another investigational drug trial
7. Pregnant females or females who have given birth within the past 90 days or who are breastfeeding
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant **unless** they are using highly effective methods of contraception during dosing and for 15 weeks after stopping treatment. Highly effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 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 patient
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF
9. Any documented history of a clinical stroke or intracranial hemorrhage, or an uninvestigated neurologic finding within the past 12 months before screening visit. Silent infarct only present on imaging is not excluded
10. Clinically significant bleeding disorder
11. Planning to undergo a major surgical procedure during the duration of the study

12a. Hospitalized within 7 days prior to Week 1 Day 1 dosing

13. Patient with active HIV infection (detectable viral load)
14. Patients with active Hepatitis B infection (HBsAg positive)

    Note: Patients with antecedent but no active Hepatitis B (i.e. anti-HBc positive, HBsAg and HBV-DNA negative) are eligible
15. 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

16. Malignant disease. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 3 years prior to study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma *in situ*
17. Concurrent severe and/or uncontrolled medical conditions which, in the opinion of the Investigator, could cause unacceptable safety risks or compromise participation in the study
18. Any condition which, in the opinion of the investigator, is likely to interfere with the successful collection of the measurements required for the study

19a. History or current diagnosis of ECG abnormalities indicating significant risk of safety such as:

- Concomitant clinically significant cardiac arrhythmias (e.g ventricular tachycardia), and clinically significant second or third degree AV block without a pacemaker
- History of familial long QT syndrome or know family history of Torsades de Pointes

20. Not able to understand and to comply with study instructions and requirements
21. Acute vaso-occlusive crisis ending within 7 days prior to Week 1 Day 1 dosing
22. Received prior treatment with crizanlizumab or other selectin targeting agent

6 Treatment

6.1 Study treatment

Crizanlizumab (SEG101) and placebo are supplied as concentrate for solution for infusion. The investigational drug is crizanlizumab (SEG101).

Following conduct of the primary analysis (once all randomized participants have reached one year of investigational treatment or discontinued within year 1), unblinding and change to an alternative dose or active treatment will be permitted for each individual participant, based on primary study results and investigator's assessment of sub-optimal efficacy vs. apparent therapy-related toxicity. Participants will receive open label crizanlizumab for the remaining period of treatment. Refer to Section 6.1.5 and Section 8.7 for further details. It is planned to observe participants for five years on investigational treatment; earlier termination of the study can be considered.

6.1.1 Investigational and control drugs

Crizanlizumab (SEG101) is supplied in individual 10 mL glass vials each containing 10.0 mL of concentrate for solution for infusion, and placebo in individual 10 mL glass vials containing 10.0 mL of solution.

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

See Table 6-1 for dose and treatment schedule.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Crizanlizumab (SEG101)	Concentrate for solution for infusion IV use	5mg/kg or 7.5mg/kg	Week 1 Day 1, Week 3 Day 1, and Day 1 of every 4-week cycle
Placebo	Concentrate for solution for infusion IV use	0.5mL/kg (no active substance)	Week 1 Day 1, Week 3 Day 1, and Day 1 of every 4-week cycle

6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Not applicable.

6.1.4 Guidelines for continuation of treatment

Not applicable.

6.1.5 Treatment duration

The total duration of treatment in the study for each participant is planned to be up to 5 years.

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

Participants who may benefit from continued investigational drug as per investigator's opinion may receive post-trial access treatment after trial completion, as indicated in Section 9.2.

6.1.5.1 Treatment beyond disease progression

Not applicable.

6.1.5.2 Treatment beyond primary analysis

Following conduct of the primary analysis, once all randomized participants have reached one year of investigational treatment or discontinued within year one, unblinding and change from placebo to crizanlizumab or alternative dose of crizanlizumab (5.0mg/kg or 7.5mg/kg) will be permitted for each individual participant.

All participants randomized to placebo will be switched to crizanlizumab. Prior to commencing treatment with crizanlizumab, these participants must meet the eligibility criteria as indicated in Section 8.7.

Decision of the dose of crizanlizumab (either 5.0 mg/kg or 7.5 mg/kg) for ALL participants will be based on primary study results and investigator's assessment of sub-optimal efficacy vs apparent therapy-related toxicity.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapies deemed necessary for the care of the participant is permitted, except as specifically prohibited. The participant must notify the study site about any new medications he/she takes within 30 days prior to initial dosing until the safety follow-up visit (through 105 days after the last dose of investigational treatment). The participants continuing crizanlizumab via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), upon completion of their EOT visit, do not have to complete the 105 days post-treatment follow-up. 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 last protocol visit must be listed on the Prior and Concomitant medications, Surgical and Medical Procedures or Transfusion page of the eCRF. Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already randomized, contact Novartis medical monitor to determine if the participant should continue participation in the study. Concomitant preventive treatment for VOC with HU/HC or L-glutamine (local HA approved medicinal product) are permitted, as per local guidelines provided the participant has been prescribed HU/HC or L-glutamine consistently over at least the 6 months and at a stable dose for at least 3 months prior to the screening visit. The dosing should not be altered or terminated, other than for safety reasons or for weight adjustments until the participant has reached one year of investigational treatment. If a physician deems it medically necessary to terminate, or alter HU/HC treatment or L-glutamine during the first year of investigational treatment, changes should not lead by default to discontinuation of the trial; however, the Novartis medical monitor must be notified.

Erythropoietin-stimulating agents are also permitted to manage chronic symptomatic anemia provided the participant has been prescribed erythropoietin-stimulating agents consistently for 6 months prior to the screening visit. The dosing should not be altered or terminated, other than for safety reasons or to maintain hemoglobin level until the participant has reached one year of investigational treatment. Aspirin, NSAIDs and prophylactic doses (as per local guidelines) of anticoagulants are permitted. Other anti-platelets agents or anticoagulants at doses targeting therapeutic levels should be used with caution (refer to Section 6.2.1.1). All approved forms of analgesics for pain are permitted as per standard of care. Other approved medications for supportive care (antiemetics, anxiolytics, hypnotics, antihistamines) are permitted, including Marinol.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Although transfusion of blood components is permitted, it is unclear how such transfusions will impact the PK/PD of crizanlizumab, so investigators are encouraged to obtain PK and PD samples before and after each transfusion session when possible. 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 HA-approved version of L-glutamine is permitted as outlined above, 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. If other forms of L-Glutamine not approved by local HA are used, the treatment information will be collected in the eCRF. Vitamin and mineral supplements (e.g. fish oil, folic acid, L-arginine, L-citrulline, magnesium, riboflavin, vitamin C, vitamin D, vitamin E, and zinc) are also permitted, though caution is advised when taking amounts exceeding 100% of the recommended daily allowance.

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

Infusion-related reactions have been reported in patients treated with crizanlizumab. Prophylactic pre-medication is permitted, and sites should follow local practice and guidelines for administration of monoclonal antibodies; pre-medications may be adjusted based on clinical presentation as deemed appropriate (e.g. for pain management). If a participant experiences a grade 3 or grade 4 IRR, study drug will be discontinued. Please refer to Table 6-3 for further guidance on management of IRRs.

Steroids should be used with caution in SCD patients. For participants presenting acute pain related to SCD, the 2020 guideline from the American Society of Hematology suggests against corticosteroids for acute pain management (Brandow et al 2020).

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

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

6.2.2 Prohibited medication

The use of other investigational drugs is prohibited during the study. In addition, the administration of monoclonal antibodies other than the investigational treatment is prohibited, due to the theoretical potential for cross-reactivity and/or overlapping toxicities with other monoclonal antibodies. If investigational agents or other monoclonal antibodies have been used in the past, they must have been discontinued at least 30 days (or 5 half-lives of that agent, whichever is greater) prior to the Screening visit. Participants that have received prior treatment with crizanlizumab are not allowed to enroll in this study. Use of approved crizanlizumab or other selectin targeting agents is prohibited during the entire study duration, both during the double blind and open label periods. New treatments to treat SCD and or to prevent/reduce VOCs are not permitted (except as outlined above) during the study.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the study site) with a sequential number suffixed to it, so that each participant 's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed.

6.3.2 Treatment assignment, randomization

At visit "Week 1" all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will complete the participant randomization form in IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participants to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

240 SCD participants will be randomized in a 1:1:1 ratio to either 5.0 mg/kg of crizanlizumab, 7.5 mg/kg of crizanlizumab or placebo. Central randomization will be stratified by HU/HC usage (yes/no) and baseline rate of VOCs leading to healthcare visit within 12 months prior to Screening visit (2-4 vs $\geq$ 5 VOCs). The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Participant, investigator staff, individuals performing the assessments, and Novartis study team (except for some selected roles indicated in Table 6-2) will remain blind to the identity of the investigational treatment from the time of randomization until the database lock for the primary analysis. An unblinded pharmacist or delegate will be responsible for the compounding of individual doses for study participants.

Unblinding will occur in the case of participant emergencies, after the primary analysis and following a treatment discontinuation if needed to ensure adequate treatment of the participant, under the oversight of Novartis. Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result the participant should be discontinued from the study treatment. The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock. Data with unblinding potential, such as Pharmacokinetics, Pharmacodynamics, [redacted] and dosing collected after the randomization visit, will be kept blind until the database lock for the primary analysis. It is the Investigator's responsibility to maintain the blind at the clinic site. In the case of an SAE or treatment discontinuation if needed to ensure adequate treatment where the Investigator deems identification of the study drug necessary, the Investigator or delegate can perform un-blinding through IRT. In addition, the unblinded pharmacist or delegate can also provide emergency disclosure of unblinding information at the site to the Investigator. This method of unblinding should only be used in emergency situations when such information might affect the course of participant treatment. In this case, the unblinding will also need to be performed retrospectively in IRT. The circumstances surrounding the breaking of the blinding code will require documentation. The Investigator should determine and document "causality" prior to unblinding the study drug. Please refer to Table 6-2 for details on data which will be assessed by independent committees in a blinded fashion.

Table 6-2 Blinding levels

	Randomization list generated	**Treatment allocation & dosing**	**Safety event (single participant unblinding)**	**Safety review**
Participants	B	B	UI	B
Site staff	B	B	UI	B
Novartis CTT	B	B	UI	B
Randomization Office	UI	UI	UI	UI
Unblinded pharmacist	UI	UI	NA	NA
Unblinded sponsor staff (examples: Clinical Trial Supply Manager, Independent Statistician, Independent Programmer, Independent Data Manager, Independent Clinical Reviewer, External Development	UI	UI	NA	UI

	Randomization list generated	Treatment allocation & dosing	Safety event (single participant unblinding)	Safety review
Operations Supplier Lead, Unblinded CRA)				
Data Monitoring Committee	UI	UI	NA	UI

UI= Allowed to be unblinded on individual participant level; B= Remains blinded; NA= Not applicable

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

If a participant does not tolerate the protocol-specified dosing schedule, dose interruptions are either recommended or mandated. Dose reductions are not allowed.

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

These dose interruptions are summarized in Table 6-3. Deviations to mandatory dose interruptions are not allowed. Permanent treatment discontinuation is mandatory for specific events as indicated in Table 6-3. Every effort should be made to maintain the participant on the protocol-defined dosing schedule. In case of dose delay for any reason, the dose should be given as soon as possible. If that infusion visit occurs within ±7 days of a protocol-scheduled visit, then the dose and all required assessments will be assigned to the nearest protocol-scheduled visit. However, if that infusion visit does not fall within ±7 days of a protocol-scheduled visit, the dose and corresponding assessments will be documented as an unscheduled visit. At that point, every effort should be made to bring the participant's infusions back onto the protocol-defined schedule (within the ±7 day window). If a participant misses 2 consecutive doses during the first year of treatment due to an ADR, the participant should be discontinued from study treatment. Participants with grade 4 ADR will be permanently discontinued from study treatment. Dose interruptions must be recorded on the Dosage Administration Record eCRF.

It is recommended that trial participants with confirmed active Coronavirus disease of 2019 (COVID-19) or presenting with symptoms indicative of COVID-19 such as fever, cough, difficulty breathing, sore throat or feeling unwell should interrupt study treatment until the trial participant has fully recovered; in case of suspected COVID-19, testing for COVID-19 is recommended as per local guidance/practice. For confirmed participants, re-testing is encouraged if signs or symptoms indicative of COVID-19 newly develop or persist. Participants with suspected infection who tested negative, may continue study treatment.

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

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

Dose interruption and re-initiation of investigational treatment	
Worst toxicity CTCAE[a] Grade (CTCAE version 5) during a cycle of therapy	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) and Grade 2 (ANC < 1.5 x 10^9/L – 1.0 x 10^9/L)	Recommendation: continue study treatment.
Grade 3 (ANC < 1.0 x 10^9/L – 0.5 x 10^9/L)	**Mandatory:** Interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists, permanently discontinue study treatment.
Grade 4 (ANC < 0.5 x 10^9/L)	**Mandatory:** Permanently discontinue study treatment.
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.3°C)	**Mandatory:** Interrupt dose until resolved or next dose schedule. If abnormality persists, permanently discontinue study treatment.
Thrombocytopenia	
Grade 1 (LPT < LLN - 75,000/mm^3) and Grade 2 (LPT < 75,000 - 50,000/mm^3)	Recommendation: continue study treatment.
Grade 3 (LPT < 50,000 - 25,000/mm^3)	Recommendation: Interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists, permanently discontinue study treatment
Grade 4 (LPT < 25,000/mm^3)	**Mandatory:** Permanently discontinue study treatment.
Investigations (Hepatic)	
Isolated Direct Bilirubin	
Grade 1 >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	Recommendation: continue study treatment.
Grade 2 and 3 (>1.5 - 10.0 x ULN if baseline was normal; >1.5 - 10.0 x baseline if baseline was abnormal)	Recommendation: interrupt study treatment. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline. Monitor for hemolysis. If resolved to ≤ Grade 1 or baseline, then continue study treatment.
Grade 4 (>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal)	**Mandatory:** Permanently discontinue study treatment.
Isolated ALT elevation	

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

Mild transient reaction; infusion interruption not indicated; intervention not indicated	Continue study treatment and increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Consider slowing the infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, opioids, IV fluids); prophylactic medications indicated for ≤24 hours	Recommendation: Temporarily interrupt infusion and increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Administer appropriate medical therapy (e.g. analgesics such as paracetamol /acetaminophen or NSAIDs and anti-histamines), as per local institutional guidelines and clinical presentation. Steroids should be used with caution unless clinically indicated (e.g. management of hypersensitivity /anaphylaxis) (Brandow et al 2020) If symptoms resolve, restart infusion per investigator discretion at a slower rate (50% rate or slower) under continuous observation. Ensure a minimum of 1-hour observation period prior to restarting the infusion. Administer premedication before restarting (e.g. analgesics such as paracetamol/acetaminophen or NSAIDs and anti-histamines) within 1 hour prior to dosing if not done already to manage the event, as per local institutional guidelines, including at subsequent infusions. In case of recurring IRRs despite premedication and prolonged infusion, discontinue study treatment.
Grade 3 and 4 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Life-threatening consequences; urgent intervention indicated	Mandatory: Permanently discontinue study treatment and initiate appropriate medical care. Collect blood sample immediately after onset of the AE for further characterization of the IRR (Section 8.5.3)

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

[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5)

[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], LDH, albumin, creatinine kinase and ALP.

6.5.2 Follow-up for toxicities

In case of a grade 3 or 4 IRR, additional blood samples will be collected as outlined in Table 6-3 and Section 8.5.3. These blood samples should be collected as soon as possible after the start of the event.

Participants whose investigational treatment is interrupted or permanently discontinued due to an adverse event must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts (e.g. ophthalmologist, endocrinologist, dermatologist, psychiatrists) should be consulted as deemed necessary. All participants must be followed up for adverse events and serious adverse events for 105 days following the last doses of investigational treatment. The participants continuing crizanlizumab via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), upon completion of their EOT visit, do not have to complete the post-treatment follow-up.

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

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

NOTE: Patients with SCD tend to have elevated transaminases, especially AST, and indirect BIL due to the hemolytic nature of this condition. Hence, ONLY ALT and Direct BIL will be required in this criteria.

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

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

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

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

In the absence of an alternative explanation, These participants should be immediately discontinued from study treatment. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions as described below:

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

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator’s responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number

- name (if available)
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.7 Preparation and dispensation

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

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

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

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

Refer to the Pharmacy Manual for further details on study drug accountability.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

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

7 Informed consent procedures

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

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

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

Novartis will provide to investigators, in a separate document, a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- Main Study Consent for parents / legal guardians to give consent for their child
- Model Participant Information and Adolescent Assent 12-17 years old for adolescents to express their understanding of the purpose of this study and what will happen to them if their parent(s)/legal guardian(s) give their consent for their participation in this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants
- Optional Off-site Research Nursing Consent to have study procedures performed at an off-site location
- Optional Off-site Research Nursing Consent for parents / legal guardians to give consent for their child to have study procedures performed at an off-site location
- Optional Adolescent Assent 12-17 years old for adolescents to express their understanding of the purpose of Off-site Research Nursing and what it means for them if their parent(s)/legal guardian(s) give their consent to have study procedures performed at an off-site location

[redacted]

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order

to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the participant will not reliably comply, then they should not be entered in the study.

The study includes an optional pharmacogenetics component which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the subjects, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent. Declining to participate in this optional assessment will in no way affect the participant's ability to participate in the main research study.

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

The participant might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The assessment schedule Table 8-1 lists all of the assessments and indicates with an "X" and "S", the visits when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) and as allowed per specified visit window. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational treatment should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

As per Section 4.6 , during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities phone calls, virtual contacts (e.g. tele consult) or visits by site staff to the participant's home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again. This telephone/virtual contact/visits to participant's home should preferably be done according to the study visit schedule.

Allowed visit windows are specified as follows:

- Screening assessments must occur within 28 days prior to the randomization
- A +/- 3 days for the visit on Day 15 (Week 3 Day 1)
- A +/- 7 days for every dosing visit (occurring every 4 weeks) from Week 7 through Week 259 (Final Dose) with a minimum of 21 days to be respected between 2 doses.
- A +/- 1 day for 336 hour post dose PK time point
- A +/- 5 days for the Phone call last infusion + 30 days
- A +/- 10 days for the Phone call last infusion + 60 days

- A + 7 days for the end of follow-up phase (last infusion + 105 days) is allowed. The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete post-treatment follow-up. Exception will be made if treatment discontinuation occurred before end of week 52, the monthly phone calls up to 1 year after first treatment will be required. If the participant will continue crizanlizumab beyond the EOT visit, via commercial supply or post-trial access, the assessments requested at EOT visit will have to be performed prior to next crizanlizumab infusion
- A +/- 10 days for the Follow-up in case of treatment discontinuation before end of Week 52

Table 8-1 Assessment schedule

Period	**Screening**		**Treatment**						
Visit Name	**Screening**	**Week 1 Day 1**	**Week 3 Day 1**	**Week 7 Day 1**	**Week 11 Day 1**	**Week 15 Day 1**		**Week 15 Day 2**	**every 4 weeks from week 19 to week 259**[1, 20]
Days	**-28 to -1**	**1 to 1**	**15**	**43**	**71**	**99**			**127 to 1820**
Weeks	**-4 to -1**	**1**	**3**	**7**	**11**	**15**			**19 to 259**
Time	**-**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**post-dose 2h**		**-**
Study drug administration		X	X	X	X	X			X
Informed consent	X								
Optional pharmacogenetic informed consent	X								
Optional informed consent for Off-site Research Nursing Visits									After W51 if patient is considered eligible for Off-Site Research Nursing visits[1]
Demography	X								
Inclusion / Exclusion criteria	X								
Confirmed diagnosis of SCD	X[2]								
Medical history/current medical conditions	X								
Sickle Cell – Vaso-Occlusive Crisis history[22]	X								
Smoking history	X								
Randomization		X							
Physical Examination	S								
Abbreviated physical exam		S	S	S	S	S			S

Period	**Screening**		**Treatment**						
Visit Name	**Screening**	**Week 1 Day 1**	**Week 3 Day 1**	**Week 7 Day 1**	**Week 11 Day 1**	**Week 15 Day 1**		**Week 15 Day 2**	**every 4 weeks from week 19 to week 259**[1, 20]
Days	**-28 to -1**	**1 to 1**	**15**	**43**	**71**	**99**			**127 to 1820**
Weeks	**-4 to -1**	**1**	**3**	**7**	**11**	**15**			**19 to 259**
Time	**-**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**post-dose 2h**		**-**
Body Height[18]	X	Annually							
Body Weight[21]	X	X	X	X	X	X			X
Vital Signs	X	X	X	X	X	X			X
Hematology[4,28]	X	X[3]	X	X	X	X[28]			X
Platelets (local)[4,34]	X	X	X	X	X	X			X
Hematology for adolescents ≤ 25kg[28]								X	
Urinalysis[4]	X	X[3]	X	X	X	X			X
Pregnancy Test (serum)	X								
Urine pregnancy test[25]		S	S	S	S	S			S
Hepatitis and HIV Screen	X								
COVID-19 Ab testing[23,27]	X[33]								Week 27 Day 1[27], Week 51 Day 1, then annually
VOC Event[5]		Continuous							
Chest X-ray	X[6]	If clinically indicated							
Hospitalization		Continuous							
Prior/concomitant medications	X	Continuous							
Prior/concomitant medications – Analgesic	X	Continuous							
Prior/concomitant medications – Anticoagulants	X	Continuous							

Period	**Screening**		**Treatment**						
Visit Name	**Screening**	**Week 1 Day 1**	**Week 3 Day 1**	**Week 7 Day 1**	**Week 11 Day 1**	**Week 15 Day 1**		**Week 15 Day 2**	**every 4 weeks from week 19 to week 259**[1, 20]
Days	**-28 to -1**	**1 to 1**	**15**	**43**	**71**	**99**			**127 to 1820**
Weeks	**-4 to -1**	**1**	**3**	**7**	**11**	**15**			**19 to 259**
Time	**-**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**post-dose 2h**		**-**
Prior/concomitant medications – Hydroxyurea/ Hydroxycarbamide	X	Continuous							
Prior/concomitant medications – L-Glutamine	X	Continuous							
Prior/concomitant medications – Erythropoietin stimulating agent	X	Continuous							
Concomitant non-drug therapies/procedures	X	Continuous							
RBC transfusion	X	Continuous							
Electrocardiogram (ECG)[7]	X	X				X	X		Week 23 Day 1, Week 47 Day 1 and then every 12 months[7]
Cardiac imaging (ECHO)	X[8]	Annually							
Adverse events/Serious adverse events	X	Continuous							
IRR[32]		Continuous							
Pharmacokinetics[9]	See Table 8-6								
Pharmacodynamics[9]	See Table 8-6								
Immunogenicity[9]	See Table 8-6								

Period	Screening		Treatment						
Visit Name	**Screening**	**Week 1 Day 1**	**Week 3 Day 1**	**Week 7 Day 1**	**Week 11 Day 1**	**Week 15 Day 1**		**Week 15 Day 2**	**every 4 weeks from week 19 to week 259**[1, 20]
Days	**-28 to -1**	**1 to 1**	**15**	**43**	**71**	**99**			**127 to 1820**
Weeks	**-4 to -1**	**1**	**3**	**7**	**11**	**15**			**19 to 259**
Time	**-**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**post-dose 2h**		**-**
Pharmacogenetic sample collection[10,31]		X[10]							
[redacted]									
Alcohol history	X								
Fetal Hemoglobin		X							Week 27 Day 1, every 3 months during the first year and then, every 6 months
Disposition	X								
Chemistry[4,29]	X	X[3]	X	X	X	X[29]			X
Chemistry for adolescents ≤ 25kg[29]								X	
Coagulation[4,30]	X	X[3]	X	X	X	X[30]			X
Coagulation for adolescents ≤ 25kg[30]								X	
[redacted]									

Period	Screening		Treatment						
Visit Name	**Screening**	**Week 1 Day 1**	**Week 3 Day 1**	**Week 7 Day 1**	**Week 11 Day 1**	**Week 15 Day 1**		**Week 15 Day 2**	**every 4 weeks from week 19 to week 259**[1, 20]
Days	**-28 to -1**	**1 to 1**	**15**	**43**	**71**	**99**			**127 to 1820**
Weeks	**-4 to -1**	**1**	**3**	**7**	**11**	**15**			**19 to 259**
Time	**-**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**pre-dose**	**post-dose 2h**		**-**
Growth and sexual maturation assessment in adolescent		X	Annually						
ECOG/ Karnofsky performance status	X								
[redacted]									
Trial Feedback Questionnaire (TFQ), optional[19]		X				X			

Period	End of Treatment (EOT)[26]	Post-treatment follow-up[26]			
Visit Name	End of Treatment (EOT)	30 Days Safety Follow-Up (Phone call)	60 Day Safety Follow-Up (Phone call)	105 Days Safety Follow-up	Monthly Follow Up 1 to Monthly Follow Up 9 (phone calls) [17]
Days	Within 7 days of last infusion	Last infusion + 30 days	Last infusion + 60 days	Last infusion + 105 days	Monthly
Weeks	260	264	268	275	N/A
Time (post-dose)	-	-	-	-	-
Study drug administration					
Informed consent					
Optional pharmacogenetic informed consent					
Demography					
Inclusion / Exclusion criteria					
Confirmed diagnosis of SCD					
Medical history/current medical conditions					
Sickle Cell – Vaso- Occlusive Crisis history					
Smoking history					
Randomization					
Physical Examination	S				
abbreviated physical exam					
Body Height	X				
Body Weight[21]	X				
Vital Signs	X			X	
Hematology	X			X	
Platelets (local)[34]	X			X	
Urinalysis	X			X	

Period	End of Treatment (EOT)[26]	Post-treatment follow-up[26]			
Visit Name	End of Treatment (EOT)	30 Days Safety Follow-Up (Phone call)	60 Day Safety Follow-Up (Phone call)	105 Days Safety Follow-up	Monthly Follow Up 1 to Monthly Follow Up 9 (phone calls) [17]
Days	Within 7 days of last infusion	Last infusion + 30 days	Last infusion + 60 days	Last infusion + 105 days	Monthly
Weeks	260	264	268	275	N/A
Time (post-dose)	-	-	-	-	-
Pregnancy Test (serum)	X			X	
Urine pregnancy test					
Hepatitis and HIV Screen					
COVID-19 Ab testing[23,27]	X				
VOC Event[5]	Continuous	X	X	X	X
Chest X-ray	If clinically indicated			If clinically indicated	
Hospitalization	Continuous	X	X	X	X
Prior/concomitant medications	Continuous			X	
Prior/concomitant medications – Analgesic	Continuous	X	X	X	X
Prior/concomitant medications – Anticoagulants	Continuous	X	X	X	X
Prior/concomitant medications – Hydroxyurea/ Hydroxycarbamide	Continuous	X	X	X	X
Prior/concomitant medications – L-Glutamine	Continuous	X	X	X	X
Prior/concomitant medications – Erythropoietin stimulating agent	Continuous	X	X	X	X
Concomitant non-drug therapies/procedures	Continuous			X	
RBC transfusion	Continuous	X	X	X	X
Electrocardiogram (ECG)	X				
Cardiac imaging (ECHO)					

Period	End of Treatment (EOT)[26]	Post-treatment follow-up[26]			
Visit Name	**End of Treatment (EOT)**	**30 Days Safety Follow-Up (Phone call)**	**60 Day Safety Follow-Up (Phone call)**	**105 Days Safety Follow-up**	**Monthly Follow Up 1 to Monthly Follow Up 9 (phone calls) [17]**
Days	**Within 7 days of last infusion**	**Last infusion + 30 days**	**Last infusion + 60 days**	**Last infusion + 105 days**	**Monthly**
Weeks	**260**	**264**	**268**	**275**	**N/A**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**
Adverse events/Serious adverse events	Continuous			X	
Pharmacokinetics[9]	See Table 8-6				
Pharmacodynamics[9]	See Table 8-6				
Immunogenicity[9]	See Table 8-6				
Pharmacogenetic sample collection[10]					
[redacted]					
Alcohol history					
Fetal Hemoglobin	X				
Disposition	X			X	X
Chemistry	X			X	
Coagulation	X			X	
[redacted]					
Growth and sexual maturation assessment in adolescent	X				
ECOG/ Karnofsky performance status					

Period	End of Treatment (EOT)[26]	Post-treatment follow-up[26]			
Visit Name	End of Treatment (EOT)	30 Days Safety Follow-Up (Phone call)	60 Day Safety Follow-Up (Phone call)	105 Days Safety Follow-up	Monthly Follow Up 1 to Monthly Follow Up 9 (phone calls) [17]
Days	Within 7 days of last infusion	Last infusion + 30 days	Last infusion + 60 days	Last infusion + 105 days	Monthly
Weeks	260	264	268	275	N/A
Time (post-dose)	-	-	-	-	-
[redacted]					
Trial Feedback Questionnaire (TFQ), optional[19]	X				

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] After first year of treatment, participant visits to the study site might be replaced by off-site visits by a qualified Research Nurse as per Section 8.6 if local settings and Novartis allow it.
[2] Confirmed diagnosis of SCD at Screening by hemoglobin electrophoresis or high performance liquid chromatography (HPLC) (performed locally)
[3] Not to be repeated on Day 1 if screening assessment took place within 72 hours
[4] Prior to every dose during year 1, prior to dosing every 3 months during year 2, prior to dosing every 6 months from year 3 to end of treatment
[5] Other APCs leading to healthcare visit and managed at home will also be collected
[6] Within 3 months of Week 1 Day 1 dosing
[7] as per Table 8-5
[8] Assessment to be done before first dosing if not done within the last 12 weeks prior to start of study drug
[9] At specified time points, blood samples will 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. The total blood volume (combining the volume needed for PK, PK, and Immunogenicity) is collected into a single serum separation tube.
[10] Whole blood will be collected for the Pharmacogenetic sample at any time during the study upon the participant's informed consent for this specific analysis purpose. Refer to Table 8-7
[11] Samples to be collected also at time of VOCs, if possible. Refer to Table 8-7
[redacted]
[16] Assessment to be done as part of the abbreviated physical examination and then at the End of Treatment and at the Follow-up visit. Refer to Section 8.5.4.1

[17] Follow-up in case of treatment discontinuation before end of week 52: Monthly phone calls up to 1 year after first treatment to follow-up and monitor VOCs/APCs leading to healthcare visit in participants who discontinued treatment during first year of treatment (including participants who continue crizanlizumab outside the study).
[18] Refer to Table 8-3

[19] Refer to Section 8.5.1

[20] After completion of primary analysis, participants randomized to placebo will be switched to crizanlizumab. Check Section 8.7 for eligibility criteria to be met prior to commencing treatment.

[21] Body weight measure is to be collected at every treatment visit so that the correct treatment dose is calculated before preparing the infusion. For treatment visits following Week 1 Day 1 visit, in order to avoid potential delays in the administration of the investigational treatment, infusion can be prepared in advance by using the participant's body weight collected at the previous treatment visit.

In all cases, body weight must be verified before dosing the participant and, if more than 5% of difference in body weight (between previous and current visit) is identified, infusion will be re-prepared using the participant's body weight collected at the current visit.

[22] Medical history of VOC includes those VOCs leading to healthcare visit (uncomplicated VOC, acute chest syndrome, priapism, hepatic and splenic sequestration events) and APCs leading to healthcare visit that the participant experienced within the 12 months prior to screening visit and also those VOCs/APCs leading to healthcare visit experienced during the screening phase ending 7 days prior to Week 1 Day 1 dosing.

[23] Additional samples to be collected according to Section 8.3.1. Samples will be collected so long as COVID-19 infections remain active within respective local geographic environment. Upon agreement between sponsor and local investigator, or once the participant is vaccinated (upon availability), the sample collection and testing may be stopped.

[redacted]

In case a patient has a grade 3 or 4 AE that is a suspected IRR, the sample should be collected as soon as possible after the start of the AE

[25] If urine pregnancy test is positive a serum pregnancy test must be performed (refer to Section 8.4.3).

[26]The participants continuing crizanlizumab upon completion of their EOT visit, via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), upon completion of EOT visit, do not have to complete the post-treatment follow-up. Exception will be made if treatment discontinuation occurred before end of week 52, the monthly phone calls up to 1 year after first treatment will be required. If the participant will continue crizanlizumab beyond the EOT visit, via commercial supply or post-trial access, the assessments requested at EOT visit will have to be performed prior to next crizanlizumab infusion. For participants discontinuing from study treatment prior to completion of W259D1 visit and continuing under crizanlizumab outside the study, and for all participants completing the W259D1 visit whether they continue on crizanlizumab outside the study or not, EOT visit should be completed 28 days +/-7 days from last dose

[27] Samples for COVID-19 Ab testing should not be collected after W23D1 for adolescents with body weight ≤ 25kg

[28] Hematology samples at W15D1 should not be collected for adolescents with body weight ≤ 25kg. They are instead collected at W15D2

[29] Chemistry samples at W15D1 should not be collected for adolescents with body weight ≤ 25kg. They are instead collected at W15D2

[30] Coagulation samples at W15D1 should not be collected for adolescents with body weight ≤ 25kg. They are instead collected at W15D2

[31] Blood sample for Pharmacogenetic testing should not be collected for adolescents with body weight ≤ 45kg

[32] Certain adverse events reported in the AE/SAE eCRF as Infusion Related Reactions will require the IRR eCRF to be completed

[33] At SCR visit, samples for COVID-19 Ab testing should not be collected on the same day when Hematology, Chemistry, Coagulation and Hepatitis/HIV samples are collected for adolescents with body weight ≤ 25kg

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

8.1 Screening

After signing the study ICF, the screening assessments will be done within 1 to 28 days prior to Week 1 Day 1. Re-screening of participants is only allowed if the participant was not randomized and treated previously. In case of re-screening, site should enter this participant as a new participant in IRT via the Rescreen form, where the original participant No. must be added. If participant has been randomized and treated, re-screening of participant is not allowed. In case re-screening occurs, all evaluations re-assessed should meet the eligibility criteria. A new informed consent form must be signed only if there is an interruption in the participant's eligibility evaluation and the investigator chooses to re-screen the participant following screen failure. If a new informed consent form is signed, AEs and medical history will be assessed relative to the new informed consent date. For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range before screen failing the participant. If the results from the central laboratory are partial or unavailable at time of the first infusion, local re-sampling from Day -14 is allowed. Specifically, for platelet count test, local sampling will be performed throughout the trial for adolescents with body weight >45kg and adults. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the participant will be considered a screening failure. An additional genetic informed consent will be available to the participant for optional participation in the pharmacogenetics part of the trial.

8.1.1 Eligibility screening

The investigator is responsible to ensure only participants who meet all inclusion and do not meet any exclusion criteria are included in the study. An eligibility question will be included on the Randomization Form available in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent but fail to be randomized for any reason will be considered a screen failure. The reason for not starting treatment will be entered on the screening phase disposition page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for SAE reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

8.2 Participant demographics/other baseline characteristics

Participant demographic characteristics, which include age, gender, self-identified race and ethnicity, will be collected. Background medical information, including diagnosis of Sickle Cell Disease and Vaso–Occlusive Crisis History, prior use of HU/HC and reason for discontinuation (as applicable), ECG, ECOG/Karnofsky performance status, relevant and current medical conditions and alcohol and smoking history will also be collected.

8.3 Efficacy

8.3.1 Efficacy assessment

Definitions

Vaso-occlusive crisis (VOC)

VOC is defined as a pain crisis (acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion) which requires therapy with oral or parenteral opioids or parenteral NSAID. Acute chest syndrome (ACS), priapism and hepatic or splenic sequestration as defined below will be considered VOC in this study.

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

1. **Uncomplicated VOC** 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 opioid or other parenteral NSAIDs, but is NOT classified as an ACS, hepatic sequestration, splenic sequestration or priapism.

   Resolution of the uncomplicated VOC:

   - An uncomplicated VOC will end once the acute pain has resolved and the pain medications given to manage the acute episode of pain have been discontinued.
   - In participants with residual pain after an uncomplicated VOC, the uncomplicated VOC will end once the acute pain has resolved such that residual pain becomes chronic, and the current pain medication regimen is used to manage the residual chronic pain.
   - For participants with chronic pain prior to onset of an uncomplicated VOC, the uncomplicated VOC will end once the participant discontinues the pain medication given to manage the uncomplicated VOC and returns back to baseline in terms of prior pain and pain medication regimen.
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, hypoxia, wheezing or cough.

   ACS will end when the participant 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 end when right upper quadrant pain has returned to baseline (pre-event) levels and hemoglobin has been stable for 24 hrs.

5. **Splenic sequestration** is 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 end when left upper quadrant pain has returned to baseline (pre-event) levels and hemoglobin has been stable for 24 hrs.

VOCs as defined above, can be managed at home or by a healthcare visit.

- **VOC leading to healthcare visit** is defined as a VOC with any visit to a medical facility such as an emergency room, hospital and/or office visit, which includes pain management of that VOC in situ.
- **VOC managed at home** is defined as a VOC with **no visit** to any medical facility and/or healthcare professional to receive treatment for VOC. Healthcare contacts for medical advice or collection of analgesic prescription in a medical facility are allowed.

  Participants should contact the Investigator (or surrogate from the site) **within 24 hours** when they believe they are experiencing a VOC that they can manage at home, both for treatment guidance and for accurate information to collect in the VOC eCRF page.

Other acute pain crises (APCs)

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

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

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

VOCs or other APCs that start within 7 days of the end of the preceding crisis event and which are considered a recurrence or continuation of the same event (e.g. based on clinical presentation and/or location) should be reported together with the preceding event as a single event. In such a case, the start and end date of this single event will be revised accordingly to cover its full duration.

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

For each visit to a medical facility for a pain episode thought to be a VOC or other APC, the following information must be documented in the eCRF: diagnostic evaluation for the episode, participant treatment, route of administration and management, course, duration of the crisis, and outcome. For participants 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.

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

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

VOC/APC leading to healthcare visit will be reviewed and determined by an Adjudication Committee (AC) comprised of independent hematologists as defined in the AC Charter.

Chest X-ray

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

Transfusions:

Participants 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 vaso-occlusive crisis is permitted and investigators are encouraged to obtain PK/PD samples before and after the simple or exchange transfusion is administered.

For participants who discontinued investigational treatment during the first year, phone calls will be scheduled monthly after treatment discontinuation to collect data over VOC/APC leading to healthcare visit up to one year following the first treatment administration. Sufficient data should be collected by the investigator to allow adjudication of these VOCs/APCs leading to healthcare visit as for any other VOC/APC occurring during the study.

Table 8-2 VOC or other APC Assessment Collection Plan

Procedure / Assessment collection plan	Screening/Baseline	During Treatment/Follow-up
Chest X-Ray[1]	Mandated	If clinically indicated
VOC or other APC information	Mandated	Mandated, when VOC or other APC occurs
Concomitant medication - Analgesics	If clinically indicated	Mandated, when VOC or other APC occurs
Healthcare resource utilization details	If clinically indicated	Mandated, when VOC or other APC occurs
Transfusion	If clinically indicated	If clinically indicated
[redacted]		

Procedure / Assessment collection plan	Screening/Baseline	During Treatment/Follow-up
Pharmacokinetic, Pharmacodynamic and Immunogenicity samples	Not Applicable	Optional at onset and resolution of VOC, fever or suspected infection. Optional before and after transfusion
[1] Within 3 months of Week 1 Day 1 dosing		

8.3.2 Appropriateness of efficacy assessments

The primary endpoint of annualized rate of VOC leading to healthcare visit is an established surrogate efficacy endpoint used for regulatory approvals. However, there is no homogeneous definition of VOC.

The definition of VOC leading to healthcare visit used in the present study is the same to the SUSTAIN study in order to have comparable results.

8.4 Safety

Safety will be monitored by assessing physical examinations, vital signs, ECG, laboratory assessments including hematology, chemistry, coagulation, urinalysis, immunogenicity and as well as collecting of the adverse events at every visit.

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

Table 8-3 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination will be performed at Screening and within 7 days following last infusion. An abbreviated (short) physical exam will include the examination of general appearance and vital signs, as well as additional components of the physical exam [redacted] 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 investigational treatment infusion. Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the participant's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the participant's eCRF.
Vital sign	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, respiratory rate and body temperature. Vital sign will be performed at screening, at all visits for which there is a scheduled investigational treatment infusion, at EOT and also at Follow up visit (last infusion + 105 days). The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. commercial drug or enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete the post-treatment follow-up.

Assessment	Specification
Body height and body weight	Height will be measured at screening in adults and adolescents, then annually and at end of treatment visit, only for adolescents. Body weight (in indoor clothing, but without shoes) will be measured at screening, at all visits for which there is a scheduled investigational treatment infusion (for dosing) and at End of Treatment visit.
Growth and sexual maturation in adolescents	Pubertal stage according to Tanner staging will be scored at Week 1 Day 1, at the end of first year of treatment (week 51 Day 1), every year and at End of Treatment visit.

8.4.1 Laboratory evaluations

Clinical laboratory analyses (hematology, chemistry, urinalysis, coagulation, hepatitis and HIV markers, COVID-19 Ab testing, serum pregnancy test and fetal hemoglobin) are to be performed centrally, unless otherwise mentioned in the schedule of assessments. Novartis must be provided with a copy of the central laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a participant 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 participants in the study and evaluating any abnormalities for clinical significance. For assessment of participants' eligibility to the study, only laboratory results from the central laboratory will be used. If the results from the central laboratory are partial or unavailable at time of the first infusion, local re-sampling from Day -14 is allowed. Specifically, for platelet count test, local sampling will be performed throughout the trial for adolescents with body weight >45kg and adults.. In such a case, eligibility may be based on the results from the local laboratory and a copy of the local lab normal ranges must be provided. The results of the local laboratory will need to be recorded in the local lab eCRF if local tests are performed during the scheduled visits (or in the unscheduled local lab eCRF if performed during unscheduled visit). Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) AE or when the treating physician cannot wait for central laboratory results for decision making. In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis. The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available, or
- Local lab results document an AE not reported by the central lab, or
- Local lab results document an AE where the severity is worse than the one reported by the central lab, or
- Eligibility had to be based on the local lab results due to pending/missing central lab results. At any time during the study up to safety follow-up, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs,

or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. The severity of laboratory data will be graded using the Common Terminology Criteria for Adverse events (CTCAE) version 5. Additional analyses are left to the discretion of the investigator.

Table 8-4 Central Clinical laboratory parameters collection plan

Test Category (***)	*Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Reticulocytes (%), Platelets*****, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, %s are acceptable))
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase ((GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea (**), Uric Acid, Amylase, Lipase, Glucose (non-fasting), estimated glomerular filtration rate (eGFR).
Urinalysis	**Macroscopic Panel** (Dipstick) will be done locally: Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, albumin, Specific Gravity, Urobilinogen **Microscopic Panel**: Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells performed, if a positive dipstick Albumin/Creatinine Ratio Microalbumin
Coagulation	PT, International normalized ratio [INR], Activated partial thromboplastin time (APTT)
Hepatitis markers	HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR, HCV Ab (at Screening only)
Additional tests	HIV Ab (at Screening only), Fetal hemoglobin, and COVID-19**** Ab (including but not limited to)
Pregnancy Test	Serum pregnancy test (at Screening, EOT and follow-up visit only), urine pregnancy test (before each infusion) will be done locally.

* Local clinical laboratory collection only where specified
** Either BUN or Urea test to be performed. It will be defined in the Laboratory manual.
*** At the discretion of the Investigator, safety laboratory tests can be performed locally before dosing (i.e, the day before or even on the same dosing day), even if not required per Protocol
****During the COVID-19 pandemic, if a participant experiences symptoms indicative of COVID-19 infection, viral testing for COVID-19 is recommended as per local guidance/practice. Please refer to lab manual for sample volume requirements and collection times for Ab testing
*****Local sampling for platelets count test will be performed throughout the trial for adults and adolescents with body weight >45kg

8.4.1.1 Fetal Hemoglobin

HbF by HPLC will be performed at the central lab to screen for hemoglobin variants in whole blood including HbA, HbS, HbC, HbF, and HbA2.

Samples will be collected at Week 1 Day 1, Week 27 Day 1, every 3 months during the first year and then, every 6 months and at the end of treatment.

8.4.2 Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed (in the supine position) after the participant has been resting for at least 5 min (10 min resting period preferred) prior to each time point indicated in Table 8-5.

Table 8-5 ECG collection plan

Visit	Time[a, b]	ECG Type
Screening (Day -28 to Day -1)	Anytime	Single 12-Lead (local ECG)
Week 1 Day 1	Pre-dose (before infusion)	Triplicate 12 Lead (central ECG)
Week 15 Day 1[c]	Pre-dose (before infusion)	Single 12-Lead (central ECG)
Week 15 Day 1[c]	2h post-dose (± 5 min)	Single 12 Lead (central ECG)
Week 23 Day 1 (6 months)	Pre-dose (before infusion)	Single 12-Lead (local ECG)
Week 47 Day 1 (12 months)	Pre-dose(before infusion)	Single 12-Lead (local ECG)
Every 12 months (until 5 years)	Pre-dose (before infusion)	Single 12-Lead (local ECG)
End of Treatment	Anytime	Single 12-Lead (local ECG)
Unscheduled with clinically significant findings	Anytime	Triplicate 12-Lead (central ECG)

[a] The exact date and time of dosing must be recorded on the appropriate eCRF. Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Additional, unscheduled 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 and sent for central review. The mean result of the central ECG analysis will be entered into the study database and used for AE reporting. Clinically significant ECG abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

[b] All post dose ECG time points are to be calculated based on the start time of the infusion.

[c] At week 15 Day 1, 2h post-dose measure is planned for steady-state. If steady-state is not achieved at week 15 Day 1, then ECG should be shifted to correlate with steady-state PK/PD sampling visit and submitted for central review. Week 15 Day 1 pre-dose ECG should still be performed at the designated visit regardless of steady-state.

8.4.2.1 Cardiac imaging - Echocardiogram

Cardiac imaging will be performed by Echocardiogram (ECHO) in order to assess the left ventricular ejection fraction (LVEF) and mean pulmonary arterial pressure (mPAP), as estimated from the tricuspid regurgitation jet velocity (TRV) if assessable, or otherwise by other formula (per institutional preference). This assessment will be performed locally, interpreted by site personnel as per Table 8-1 and documented on the eCRF page containing information on LVEF, TRV, (estimated) mPAP and an overall assessment in case abnormal findings.

Each echocardiography must be kept in the source documents at the study site. Clinically significant Echo abnormalities present at screening when the participant signed informed consent should be reported on the Medical History eCRF page.

New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

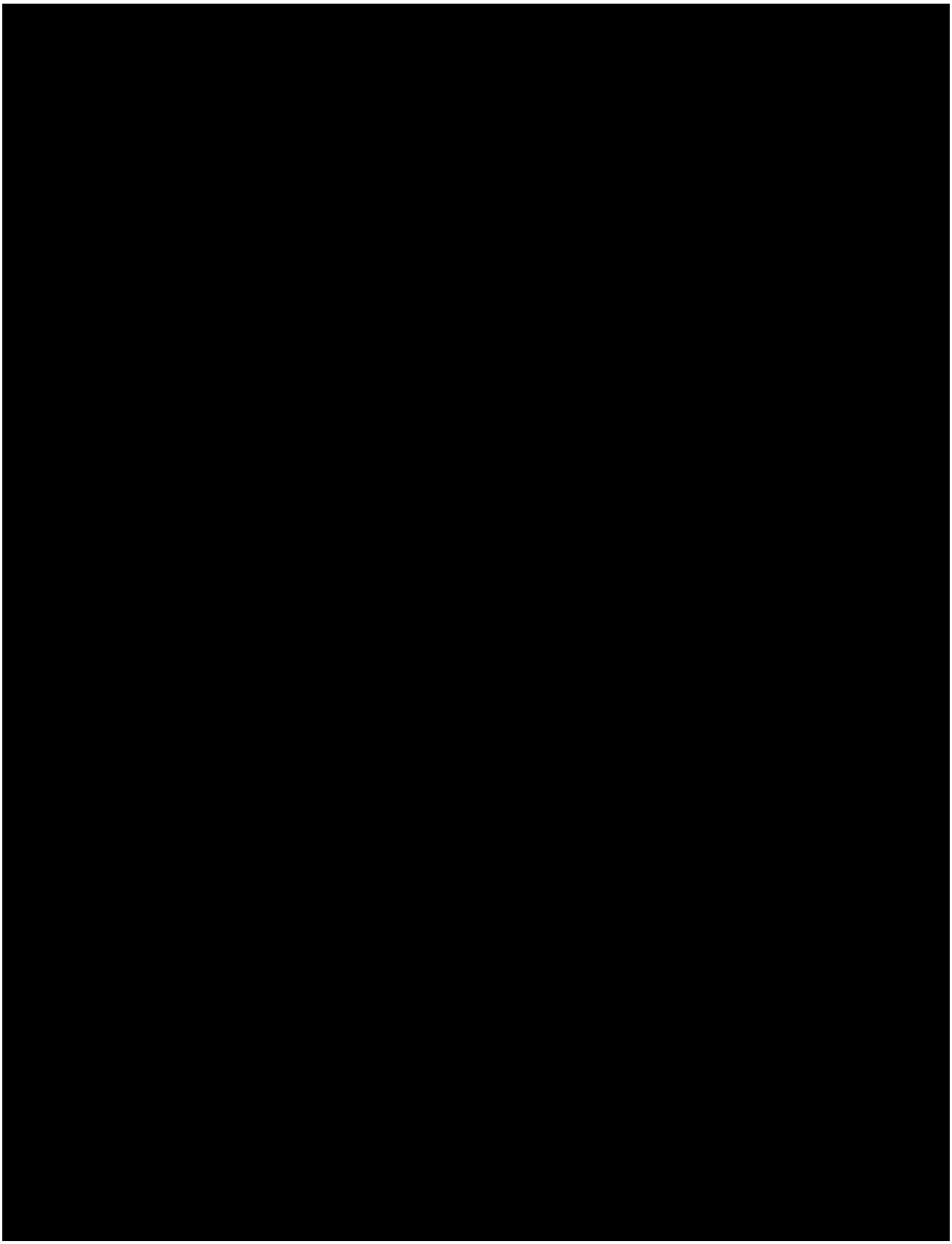
8.4.3 Pregnancy and assessments of fertility

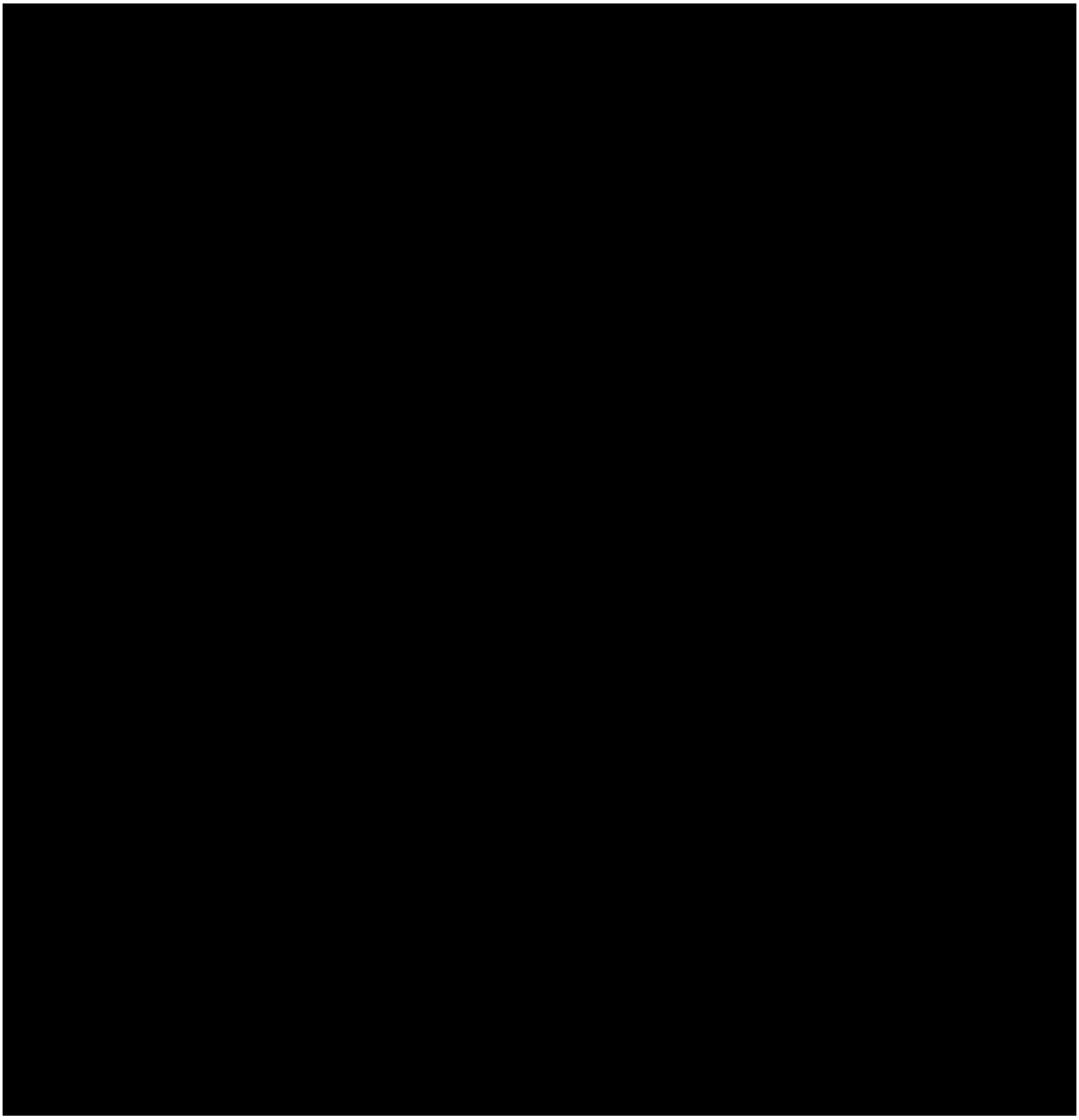
All female participants of childbearing potential and pre-menopause who are not surgically sterile must perform serum hCG pregnancy testing at screening in order to confirm study eligibility. Additional pregnancy testing might be performed if requested by local requirements.

Serum pregnancy testing is required at screening, at the EOT visit and at the end of the follow up visit. During the study, urine pregnancy testing will be performed locally prior to each dosing. The positive urine test needs to be confirmed with serum test. If positive, the participant must be discontinued from study treatment.

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

8.5 Additional assessments





Trial Feedback Questionnaire (TFQ)

This trial will include an option for participants to complete an anonymized questionnaire, 'Trial Feedback Questionnaire' at Week 1 Day 1, Week 15 Day 1 and EOT. The intention of this questionnaire is to collect participant feedback on their clinical trial experience. Individual participant level responses will NOT be reviewed by investigators. Novartis will use these responses to understand where improvements can be made in the clinical trial process. This questionnaire DOES NOT collect data about the participant's disease, symptoms, treatment effect or adverse events, and therefore would not be trial data.

8.5.2 Pharmacokinetics

Serial blood samples will be collected from all participants to assess PK/PD/IG 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 12.5.3 for a table of PK parameters that will be derived. Additionally, when possible and appropriate, PK/PD/IG samples should be collected at the time of onset and resolution of VOC event, fever, or suspected infection and at the time of transfusion (prior to and ≥ 24 hours after each of the listed events).

8.5.2.1 Pharmacokinetics, pharmacodynamics, and immunogenicity blood collection and handling

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

For PK/PD/IG samples, blood draws will be collected into serum separator tubes (without anticoagulant) and allowed to clot for 30 minutes (undisturbed) at room temperature. The tubes will be centrifuged for 10 minutes at approximately 3000 x g in order to separate serum. Each serum sample will be aliquoted and transferred into freezer-proof polypropylene screw-cap tubes (2 tubes for PK, 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 at -70ºC in an upright position until shipment and analysis.

Each serum samples should be labeled with the appropriate study, center, and participant numbers, as well as the sequential PK/PD/IG samples 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. On days and time points where blood PK/PD/IG samples are to be drawn, the PK samples must be drawn first. The exact date and time of dosing, as well as the date and actual time of blood sampling must be recorded on the appropriate eCRF. Sampling problems will be noted in the relevant field of eCRF.

Refer to the [CSEG101A2301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK/PD/IG samples.

Table 8-6 Pharmacokinetics, pharmacodynamics, and immunogenicity blood collection log

Week	Day	Scheduled time point following initiation of infusion[a]	PK collection number/Dose reference ID		PK Sample No	PD sample No[b]	IG sample No	Sample volume (mL)
1	1	Pre-dose	1	--	1	101	201	7.5
1	1	0.5h[g] (± 10 min; end of infusion)	1	--	2	--	--	2.5
1	1	2h (± 30 min)	1	--	3	102[h]	--	5

Week	Day	Scheduled time point following initiation of infusion[a]	PK collection number/Dose reference ID		PK Sample No	PD sample No[b]	IG sample No	Sample volume (mL)
1	1	4h (± 30 min)	1	--	4	--	--	2.5
1	2	24h (± 2h)	1	--	5	103	--	5
1	4	72h (± 2h)	1	--	6	104	--	5
2	1	168h (± 24h)	1	--	7	105	--	5
3	1	Pre-dose[e]	2	101[c]	8	106	202	7.5
7	1	Pre-dose[e]	3	201[c]	9	107	--	5
11	1	Pre-dose[e]	4	301[c]	10	108	--	5
15[d]	1	Pre-dose[e]	5	401[c]	11	109	203	7.5
15[d]	1	0.5h[g] (± 10 min; end of infusion)	5	--	12	--	--	2.5
15[d]	1	2h (± 30 min)	5	--	13	110	--	5
15[d]	1	4h (± 30 min)	5	--	14	--	--	2.5
15[d]	2	24h (± 2h)	5	--	15	111	--	5
15[d]	4	72h (± 2h)	5	--	16	112	--	5
16[d]	1	168h (± 24h)	5	--	17	113[h]	--	5
17[d]	1	336h (± 24h)	5	--	18	114	--	5
18[d]	1	504h (± 24h)	5	--	19	115[h]	--	5
19[d]	1	Pre-dose[e]	6	501[c]	20	116	204[h]	7.5
23	1	Pre-dose[e]	7	601[c]	21	117	--	5
27	1	Pre-dose[e]	8	701[c]	22	118	205	7.5
51	1	Pre-dose[e]	9	801[c]	23	119	206	7.5
75	1	Pre-dose[e]	10	901[c]	24	--	207	5
99	1	Pre-dose[e]	11	1001[c]	25	--	208	5
147	1	Pre-dose[e]	12	1101[c]	26	--	209	5
195	1	Pre-dose[e]	13	1201[c]	27	--	210	5
243	1	Pre-dose[e]	14	1301[c]	28	--	211	5
End of Treatment (EOT)	1	--		1401	29	--	212	5
Follow up	1	--	--	1501	30	--	213	5

Week	Day	Scheduled time point following initiation of infusion[a]	PK collection number/Dose reference ID		PK Sample No	PD sample No[b]	IG sample No	Sample volume (mL)
(Last infusion + 105 days)								
Unscheduled Sample[f]	Anytime	--	--	--	1001+	2001+	3001+	7.5

[a] Scheduled PK/PD/IG time points are relative to the start of infusion of crizanlizumab. All blood samples are to be collected from the arm opposite from the investigational drug infusion. On days and time points where blood PK/PD/IG samples are to be drawn, the PK samples must be drawn first.
[b] PD: P-selectin inhibition
[c] For any PK pre-dose samples (sample numbers 8-11, 20-29), the actual date and time of administration of the previous dose of study medication (therapy) should also be recorded with appropriate Dose reference IDs as indicated in the above table.
[d] Sampling to occur at steady-state (week 15). If dose is interrupted (missed dose) or an infusion is delayed beyond the visit day before week 15, the steady-state sampling will occur after the dose has been resumed and at least 3 consecutive infusions have been given without interruption.
[e] Within 24 hours before dose administration
[f] Including at onset and resolution of VOC event, fever, or suspected infection and at the time of transfusion (prior to and ≥ 24 hours after each of the listed events), if feasible.
[g] The 0.5h sample is intended for collection at end of typical 0.5h infusion. In the instance that infusion time is prolonged beyond 0.5h (for example if infusion is completed at 1h, then 0.5h sample will not be collected and end of infusion sample will be collected at 1h, if the end of the infusion is within collection window of 2h PK/PD sample then collection of 2h PK/PD sample is not required). Maximum allowed infusion time to allow PK/PD profile sampling is 2h, beyond which PK/PD sampling for profile purpose will not proceed. However, despite the delay in infusion, if the full dose is administered at the visit day then multiple dose PK/PD profile sampling may occur at week 15. In this case, pre-dose PK/PD sampling at weeks 3, 7 or 11 will still need to be collected.
[h] W1D1 PD 2h sample number 102, W16D1 PD sample number 113, W18D1 PD
sample number 115, W19D1 IG sample number 204 should not be collected for adolescents with weight ≤ 25 kg. The blood volume for adolescent with body ≤ 25 kg is is aligned with EMA guideline 2017

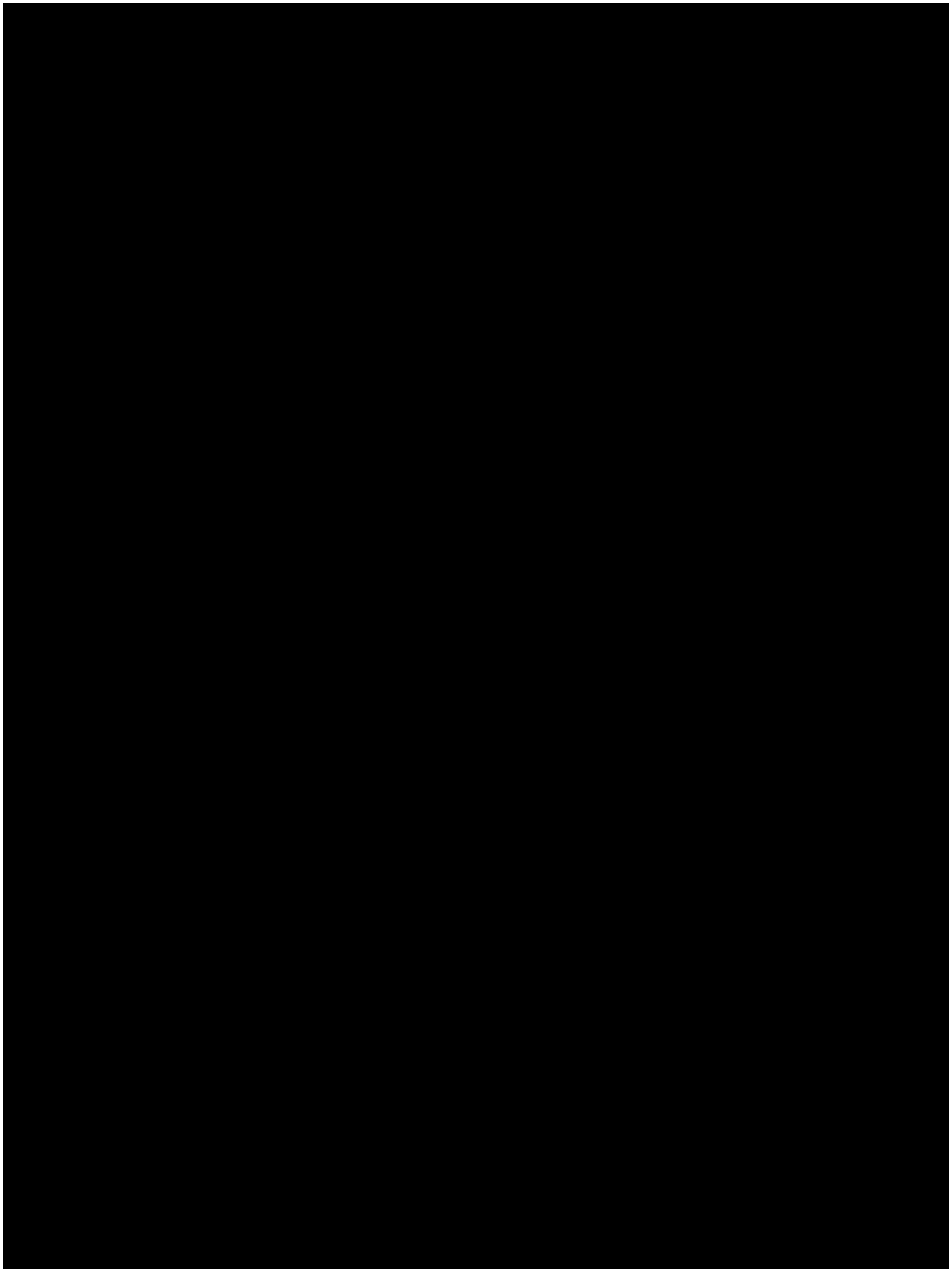
8.5.2.2 Analytical method

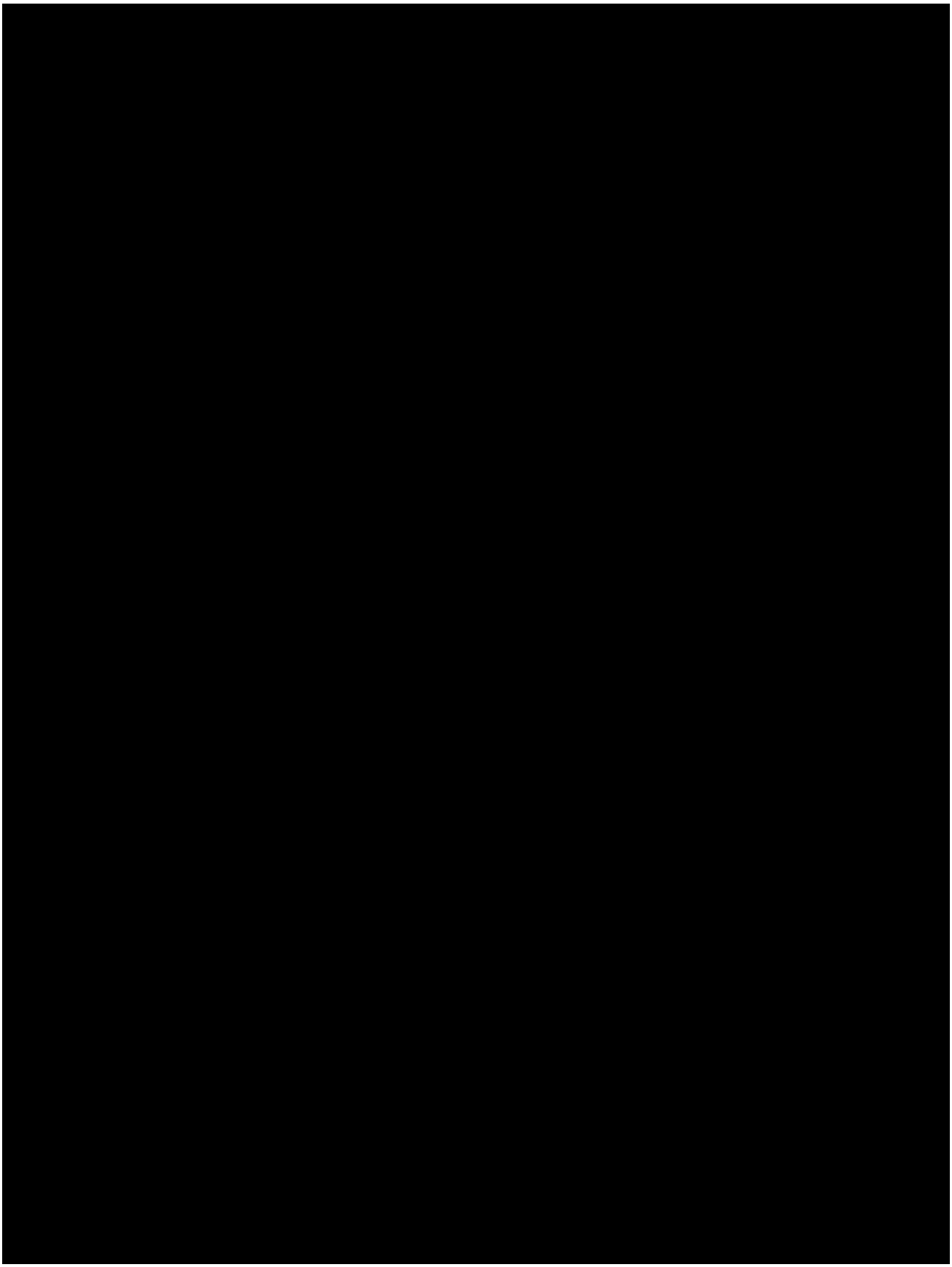
The crizanlizumab PK assay is a target capture ELISA to determine the concentration of crizanlizumab remaining in serum samples. Concentrations below the lower limit of quantification (LLOQ) will be reported as 0.00 µg/mL and missing samples will be labeled accordingly.

A pharmacodynamic (PD) 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 is 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.





8.6 Participant Off-site research nursing visits

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to Table 8-1 performed at an off-site location. The off-site location is not a site location where the investigator will conduct the trial and where source data will be maintained, but is for example the participant's home or another safe location. Suitability for the off-site location will be assessed by the Off-site Research Nurse (ORN) and ultimately decided by the investigator.

These off-site visits will involve a qualified ORN who will visit the participant to perform study procedures according to Table 8-1 under delegation of the investigator. The investigator will retain accountability for participant oversight and all medical decisions (i.e. protocol specified medical procedures, AE/SAE assessment and reporting, changes in medication, etc.). The rationale for the optional off-site visits is to unburden the participant by reducing the number of times they are required to travel the study site.

The off-site visits will be offered in certain countries and sites as determined by Novartis. Off-site visits may replace on-site visits if Novartis, investigator and local regulations and conditions allow.

Procedures can be conducted in an off-site location after one year on treatment if agreed between investigator, participant, and Novartis. Off-site visits may only occur if they can be done without affecting the wellbeing of the participant during the study and with the same level of scientific integrity as assessments conducted on-site.

The following conditions must be met for infusion of investigational treatment to occur at an off-site location:

- The participant must have completed one year of treatment on-site (up to and including week 51 day 1).
- At least the last 3 consecutive infusion visits must have occurred on-site without any AE Grade 3 or higher (possibly related to study treatment) or Grade 2 IRR and/or any concurrent medical conditions which, in the opinion of the investigator, could cause unacceptable safety risks.
    - Where a participant has begun off-site visits and an AE Grade 3 or higher (possibly related to study treatment) or Grade 2 IRR and/or any concurrent medical conditions which, in the opinion of the investigator, could cause unacceptable safety risks occurs, the participant must resume the on-site visits until the above condition is met
    - Where a participant switches from placebo to crizanlizumab following conduct of the primary analysis and unblinding of the study, the participant must resume/continue the on-site visits until the above condition is met for the treatment with crizanlizumab
- The investigator must consider that emergency services are adequately accessible to the participant within a reasonable timeframe in order to treat any potential SAEs during the Off-site Research Nursing visit.

The participants are under no obligation to participate in off-site visits, as they can decide to continue with on-site visits at the study site. Participants that the investigator identifies as suitable as per the Off-site Study Operational Manual and who may benefit from off-site visits must provide consent in the optional Off-site Research Nursing Informed Consent.

Participants have the right to revert to attend all, or specific, study visits on-site at the study site at any time. The investigator and Novartis also have the right to revert all, or specified, study visits to be performed on-site at the study site instead of off-site.

Some on-site visits are expected when the investigator (or delegated study physician) needs to physically see the participant or study procedures can only be performed on-site. It is recommended that on-site visits occur every 3rd month during the participants second year of study treatment, and every 6th month during the participants 3rd, 4th and 5th years of study treatment when sample collection is scheduled. The on-site visit schedule will be determined in discussion between the participant, investigator, and Novartis.

The information if a visit was conducted at an off-site location must be recorded on the visit date eCRF.

The off-site visits will use a third-party vendor centrally sourced by Novartis that can provide qualified research nurses to perform study assessments. Investigator-delegated activities performed by the ORN will be under the oversight of the investigator who will be responsible to confirm that the ORN is adequately qualified and trained. The investigational treatment will be compounded according to the Pharmacy Manual. Shipping of investigational treatment will be under controlled conditions to be received by the qualified ORN for administration to the participant. The ORN will be blinded according to Section 6.4.

Where off-site visits are offered to participants and if allowed by local regulations, Novartis may offer an approved third party Telemedicine platform to investigators, ORNs and participants to support the management and communication of the off-site research activities. The use of the platform is recommended for off-site visits as the provided software interface allows the investigator/delegate to connect securely via video call with the ORN and the participant during the off-site visit, if agreed by the participant. In addition, both site personnel and ORN can securely upload electronic copies of helpful information to facilitate the planning and conduct of the off-site visits. Site personnel may also share, where locally applicable, IRB/IEC/HA-approved educational materials with participants through the digital application, if agreed by the participant and the investigator. As ensuring data privacy and security is essential, the selected telemedicine platform uses measures such as data encryption, access controls and audit trails to ensure integrity, reliability and security of data flow.

More details of the off-site research nursing and telemedicine processes are outlined in a separate Off-site Study Operational Manual that will be provided to the sites participating in the off-site research nursing visits.

8.7 Eligibility criteria for participants who switch from placebo to crizanlizumab after primary analysis

After completion of primary analysis (see Section 6.1.5.2), all participants randomized to placebo will be switched to crizanlizumab. Prior to commencing treatment with crizanlizumab, these participants must meet the following eligibility criteria:

- ECOG performance status ≤ 2.0 for adults and Karnofsky ≥ 50% for adolescents
- Participants must meet the following central laboratory values. In case of re-sampling needed, local laboratory values are allowed. Refer to Section 8.4.1 for further details:
  - Absolute Neutrophil Count ≥ 1.0 x 10^9/L
  - Platelet count ≥ 75 x 10^9/L
  - Hemoglobin: for adults (Hb) ≥ 4.0 g/dL and for adolescents (Hb) ≥ 5.5 g/dL
  - Glomerular filtration rate ≥ 45 mL/min/1.73 m2 using CKD-EPI formula in adults, and Schwartz formula in adolescents
  - Direct (conjugated) bilirubin < 2.0 x ULN
  - Alanine transaminase (ALT) < 3.0 x ULN
- Participants with concurrent severe and/or uncontrolled medical conditions which, in the opinion of the Investigator, could cause unacceptable safety risks must not initiate crizanlizumab.

If the participant has not undergone these specific lab assessments 14 days prior to commencing treatment with crizanlizumab, they must be completed via an unscheduled visit in order to ensure the participant meets the eligibility criteria. NOTE: An additional visit to allow the loading dose at a 2 week interval after the initiation of crizanlizumab must take place. Additional, unscheduled lab assessments can be performed at the discretion of the investigator as clinically indicated.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). **When possible, they should return for the follow up visit**. If they fail to return for the follow up visit for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

In addition to mandatory discontinuation reasons for study treatment listed in Section 6.5.1, study treatment **must** also be discontinued under the following circumstances:

- Pregnancy
- Lactation
- Participant/Guardian decision
- Unsatisfactory therapeutic effect
- Grade 4 AE and dose interruptions of investigational treatment due to toxicity (see Section 6.5)
- Use of prohibited medication (see Section 6.2.2)
- Emergency unblinding before Primary Analysis, as described in Section 6.6.2
- Any other protocol deviation that results in a significant risk to the participant's safety
- Other reason for earlier termination may include but are not limited to:
  - Decision based on recommendations from applicable board(s) after review of safety
  - Discontinuation of study drug development

For participants who discontinue treatment during the first year (including participants who continue crizanlizumab outside the study), phone calls will be scheduled monthly after treatment discontinuation to collect data over VOCs/APCs leading to healthcare visit up to one year following the first treatment administration. Sufficient data (as specified in the adjudication charter) will be collected by the investigator to allow adjudication of these VOCs/APCs as any other VOC/APC occurring during the study.

Following the treatment discontinuation, participants will perform an End of Treatment visit. If a participant misses 2 consecutive doses due to an ADR during the first year of treatment, the participant should be discontinued. Permanent treatment discontinuation is mandatory for specific events indicated as indicated in Table 6-3. All participants must be followed up for adverse events and serious adverse events for 105 days following the last doses of crizanlizumab. The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete post-treatment follow-up. If the participant will continue crizanlizumab beyond the EOT visit, via commercial supply or post-trial access, the assessments requested at EOT visit will have to be performed prior to next crizanlizumab infusion. For participants discontinuing from study treatment prior to completion of W259D1 visit and continuing under crizanlizumab outside the study, and for all participants completing the W259D1 visit whether they continue on crizanlizumab outside the study or not, EOT visit should be completed 28 days +/-7 days from the last dose.

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples) and
- No longer wishes to receive study treatment and
- Does not want any further visits or assessments (including further study-related contacts).

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

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

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

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

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

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (provide instruction for contacting the

participant, when the participant should stop taking drug, when the participant should come for a final visit) and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

The study will be completed when all the randomized participants have either completed or discontinued the study treatment and/or the 105 days follow-up period. The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete post-treatment follow-up. Exception will be made if treatment discontinuation occurred before end of week 52, the monthly phone calls up to 1 year after first treatment will be required.

The final analysis will occur when the study is completed. All available data from all participants up to the trial end will be analyzed and summarized in a final CSR.

Novartis will provide crizanlizumab to participants who may benefit from continued treatment as per the Investigator's opinion after study completion until the earliest occurrence of the following:

- Crizanlizumab is commercially available and reimbursed in the participant's country for this participant population, and participants are eligible to be prescribed the commercial drug
- Another clinical study becomes available that can continue to provide crizanlizumab in this participant population and ongoing participants are eligible to be transferred to that clinical study
- Participant is no longer deriving benefit per the investigator's evaluation.

Safety will be monitored and reported to Health Authorities per regulatory requirements.

10 Safety monitoring and reporting

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe the participant to visit the site again. This telephone/virtual contact should preferably be done according to the study visit schedule, or more frequently if needed.

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

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

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

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

1. The Common Toxicity Criteria (CTC) AE grade (version 5).

   Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.
2. Its relationship to the study treatment. If the event is due to lack of efficacy the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy are not caused by the trial drug, they happen in spite of its administration and/or a lack of efficacy can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.

   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Drug interrupted/withdrawn
6. Its outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

   If the event worsens, it should be reported a second time in the eCRF 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 eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

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

Adverse event monitoring should be continued for at least 105 days following the last dose of study treatment. The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete post-treatment follow-up.

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

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

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

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

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- social reasons and respite care in the absence of any deterioration in the participant's general condition
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 105 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete post-treatment follow-up. SAEs occurring after the participant has provided informed consent until the time the participant is deemed a screen failure must be reported to Novartis.

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

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode

within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow-up information is submitted in the same way as the original SAE Report and should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the participant continued or withdrew from study participation.

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

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees (EC) in accordance with EU Guidance 2011/C172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 105 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment. The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete post-treatment follow-up.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

Refer to Section 6.5.2.1 Follow-up on potential drug-induced liver injury (DILI) cases.

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

10.2.2 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data and recommend to Novartis whether to continue, modify, or terminate a trial.

The DMC will consist of clinicians specialized in sickle cell disease and a biostatistician. Details of the role of the DMC will be described in the DMC charter.

10.2.3 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the clinical trial and Novartis representatives from the Clinical Trial Team. The SC will ensure transparent management of the study according to the protocol. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop

recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in the Steering Committee charter.

10.2.4 Adjudication committee

All VOCs/APCs leading to healthcare visit will be reviewed and confirmed by an Adjudication Committee. The AC will be comprised of independent hematologists specialized in the treatment of SCD, to ensure consistency across study sites and to allow for an unbiased endpoint assessment.

All personnel involved in the adjudication process will remain blinded to participant information and treatment allocation. Specific details regarding the adjudication and endpoint definitions will be described in the AC charter.

Case-by-case results of the adjudications will not be communicated to the sites. Consistency between investigator assessment and AC assessment of the VOC will be reviewed on an ongoing basis. Additional guidance may be provided to investigator in case of inconsistencies.

10.3 Protocol Exempt AEs & SAEs

Protocol Exempt AEs & SAEs are implemented in the SEG101 program. VOCs and other APC must be reported on the VOC/other APC page in the eCRF. As VOCs and other APCs are considered endpoints for the purpose of evaluation of efficacy, AEs and SAEs involving VOCs or other APCs SHOULD NOT be reported as AEs or SAEs for the purpose of this study. These events will not be considered as SAEs in regards to reporting requirements. Procedures which are directly related to the VOC, e.g. ventilation of a participant with acute chest syndrome are considered part of the VOC and will not be reported as AE/SAEs but entered in the eCRF-page "concomitant non-drug therapies/procedures". Additional events or complications which are not VOCs itself will be reported as AE/SAEs. Details will be given in the eCRF-completion guidance.

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

The events in Section 8.3 are the VOCs and other APCs that will not be reported as AEs/SAEs.

In case a VOC/APC event is suspected to be related to study treatment, and/or resulting in a fatal outcome, it will be reported as AE/SAE in addition to the VOC/acute pain crisis eCRF page.

11 Data Collection and Database management

11.1 Data collection

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

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 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, allow modification and/or verification of the entered data by the investigator staff.

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

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

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study primary analysis or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician before the primary analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several

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

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

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

12 Data analysis and statistical methods

For this study, there are two main analyses: the primary analysis and the study completion analysis.

The cut-off date for primary efficacy and safety analyses will be defined as the date where all randomized participants have reached one-year of treatment or discontinued within year 1.

After the primary analysis, there will be no formal comparison of 7.5 mg/kg and 5.0 mg/kg respectively versus placebo since dose change or treatment change is allowed. However, the long term efficacy and safety after year 1 will be evaluated through efficacy and safety assessments by group (5.0 mg/kg only, 7.5 mg/kg only, placebo only, at least one dose escalation in the group with starting dose of 5.0 mg/kg, at least one dose reduction in the group with starting dose of 7.5 mg/kg, treatment change to 5.0 mg/kg in the group with starting treatment of placebo, treatment change to 7.5 mg/kg in the group with starting treatment of placebo). Periods defined based on pre- and post- switch of treatment/dose will be considered for the analyses. The analyses after the primary analysis will be descriptive and exploratory. The analysis will be performed when the study is complete. Hence, it is referred to as the "study completion analysis."

In addition to the two main analyses, safety DMC analyses will also be performed prior to the primary analysis.

The following sections will focus on the primary analysis.

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

12.1 Analysis sets

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

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

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

- participant 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
- participant provides at least one PK parameter
- participant 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 participants 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.

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

- participant 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
- participants provides at least one PD-AUC (single dose or multiple dose) parameter
- participant 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 participants 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.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS.

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

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

12.3 Treatments

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

The duration of exposure to investigational treatment (in months) 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.

The number of participants with dose adjustments (interruption,) and the reasons will be summarized by treatment group and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system and by treatment group.

12.4 Analysis of the primary endpoint(s)

The primary objective is to compare the efficacy of 7.5 mg/kg and 5.0 mg/kg of crizanlizumab respectively versus placebo (in addition to standard of care) for preventing VOCs leading to healthcare visits over the first year post randomization in SCD patients 12 years and older at the time of study entry. The primary analysis cut-off date will be defined as the date by which all randomized participants have reached one-year of investigational treatment or discontinued within Year 1.

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the annualized rate of VOC events leading to healthcare visit in each treatment group over the first year post randomization. The annualized rate of VOC is the number of VOCs multiplied by 365 and divided by the number of days in the observation period. VOCs leading to healthcare visit will be reviewed and confirmed by an AC comprised of independent hematologists.

12.4.2 Statistical model, hypothesis, and method of analysis

The scientific objective guiding the primary analysis is to estimate the treatment effect of crizanlizumab compared to placebo, for the target population on the annualized rate of VOC leading to healthcare visit. The treatment effect of interest shall be defined as:

- on treatment over one year
- without initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin) over the first year post randomization
- and regardless of intake of analgesic (including opioids) or ad hoc transfusions administered temporarily

The primary efficacy endpoint, annualized rate of VOC leading to healthcare visit, will be analyzed based on the data from the FAS according to the treatment arm and the stratification factors participants were randomized to. In line with the treatment effect of interest, the primary observation period will include only data before study treatment discontinuation and before initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin); while data after intake of analgesic (including opioids) or ad hoc transfusions administered temporarily until one year post randomization, will be included.

More details will be provided in a standalone document, defining the estimands.

A negative binomial regression model with treatment and randomization stratification factors as covariates will be used for analysis, with the logarithm of observation time as offset. The estimates of annualized VOC rates between treatment groups and their 95% confidence intervals will be provided.

To control the overall family-wise type I error rate (FWER) an appropriate multiplicity adjustment procedure using a closed testing strategy will be applied to the analyses of the primary and key secondary endpoints for the 2 doses comparisons to placebo. This strategy to preserve the overall FWER at $\alpha = 5\%$ (two-sided) is described in Section 12.5.1.

Pairwise comparison of the 7.5 mg/kg and 5.0 mg/kg crizanlizumab annualized rate of VOC leading to healthcare visit will be performed against the placebo. The following hypotheses will be tested:

The primary statistical null hypotheses are:

- H_0(7.5 mg/kg): there is no difference between crizanlizumab 7.5 mg/kg and placebo groups with respect to the annualized rate of VOCs leading to healthcare visit over the first year post randomization
- H_0(5.0 mg/kg): there is no difference between crizanlizumab 5.0 mg/kg and placebo groups with respect to the annualized rate of VOCs leading to healthcare visit over the first year post randomization

These hypotheses will be tested using the Wald test statistic within generalized linear model assuming a negative binomial distribution and will compare 7.5 mg/kg and 5.0 mg/kg crizanlizumab versus placebo at the appropriate α-level adjusted considering multiple testing (as described in Section 12.5.1).

12.4.3 Handling of missing values/censoring/discontinuations

By using as primary endpoint the annualized rate of VOCs leading to healthcare visit, the intrinsic assumption is that the frequency of VOCs before treatment discontinuation would have been observed also for the entire first year of treatment. Supportive analyses are exploring different assumptions to handle missing data (Section 12.4.4).

12.4.4 Sensitivity and Supportive analyses

Supportive analyses

For the supportive analysis 1, the treatment effect regardless of treatment discontinuation, initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin) during year 1 is of interest. Consequently, data collected after these events and before the end of year 1 will be included. For the supportive analysis 2, different imputation methods will be used for different reasons for treatment discontinuation and other events mentioned above. For the supportive analysis 3, all the VOCs collected until the primary analysis cut-off and before treatment discontinuation and initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin) will be included. Details of the supportive analyses will be provided in a standalone estimand document.

The same analyses as for the primary analysis will be repeated for the supportive analyses.

The time to treatment discontinuation and the time to initiation or discontinuation of HU/HC or L-Glutamine (or other treatments to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin) will be summarized using Kaplan-Meier methods.

Some subgroup analyses of the primary efficacy endpoint are planned by the following subgroups, if there is enough participants in each category allowing such analysis:

- Categorized Crisis (VOC) History: 2-4 and ≥ 5
- HU/HC Use: YES and NO
- Genotype: HbSS and HbSβ^+ /HbSC/HbSβ^0 /Other
- Gender: Male and Female
- Ethnicity: the subgroups of ethnicity will be defined in the SAP
- Age: 12-<18, ≥18 years
- Race: the subgroups of race will be defined in the SAP

12.5 Analysis of secondary endpoints

The key secondary objective is to assess the annualized rate of all VOCs (managed at home + leading to healthcare visit) over the first year post randomization. Other secondary objectives over the first year post randomization include annualized rate of VOCs managed at home, rate of participants free from VOC leading to healthcare visit, time for first and second VOC leading to healthcare visit, duration of VOC leading to healthcare visit, healthcare resource utilization (visits to clinic, ER, hospitalizations), SCD-related renal damage and PK and PD (P-selectin inhibition). Another set of secondary objectives will evaluate the long-term efficacy, safety and immunogenicity of crizanlizumab not only over the first year post randomization but over the entire study period.

Secondary efficacy endpoints will be analyzed using the FAS. For all safety analyses the safety set will be used.

12.5.1 Efficacy endpoint(s)

The key secondary efficacy endpoint is the annualized rate of all VOCs (managed at home + leading to healthcare visit) over the first year post randomization. VOCs managed at home reported in the eCRF and VOCs leading to healthcare visit assessed by AC will be considered.

The analysis method used in the primary endpoint will be utilized for the key secondary endpoint.

To ensure control of FWER of $\alpha = 5\%$ (two-sided), the closed testing procedure will account for testing the primary (H1 for 7.5 mg/kg vs. Placebo and H2 for 5.0 mg/kg vs. Placebo) and key secondary endpoints (H3 for 7.5 mg/kg vs. Placebo and H4 for 5.0 mg/kg vs. Placebo) for each of the 2 doses comparisons to placebo, being a total of 4 hypotheses:

- H1 for the primary endpoint comparison between 7.5 mg/kg and Placebo
- H2 for the primary endpoint comparison between 5.0 mg/kg and Placebo
- H3 for the key secondary endpoint comparison between 7.5 mg/kg and Placebo
- H4 for the key secondary endpoint comparison between 5.0 mg/kg and Placebo

Any intersection hypothesis will be tested by either a Dunnett-test or a Bonferroni-test (depending on whether the correlation is known or not) or a single test as described in Table 12-1. All intersections which contain H1 and H2 (including the global hypothesis that all 4 hypotheses are true) will be tested by the Dunnett test of H1 and H2. All intersections which contain (H1 and H4) or (H2 and H3) will be tested by the Bonferroni-test splitting alpha between H1 and H4 or H2 and H3, respectively. All intersections which contain H3 and H4 will be tested by the Dunnett test. All other tests will use full level alpha test. As per the closure principle, a given hypothesis Hi (with i=1, 2, 3, 4) will be rejected if all intersections it is in, are also rejected. In other words, the adjusted p-value will be the maximum of the p-values from all intersection tests in which Hi is included. The key secondary endpoint of a given dose will be tested only if the difference in the primary endpoint for the same dose is statistically significant.

Table 12-1 Intersection hypotheses and local significance levels

Intersection hypotheses	Test	H_1	H_2	H_3	H_4
$H_1 \cap H_2 \cap H_3 \cap H_4$	Dunnett	α*	α*	0	0
$H_1 \cap H_2 \cap H_3$	Dunnett	α*	α*	0	-
$H_1 \cap H_2 \cap H_4$	Dunnett	α*	α*	-	0
$H_1 \cap H_2$	Dunnett	α*	α*	-	-
$H_1 \cap H_3 \cap H_4$	Bonferroni splitting alpha	α/2	-	0	α/2
$H_1 \cap H_3$	Full level	α	-	0	-
$H_1 \cap H_4$	Bonferroni splitting alpha	α/2	-	-	α/2
H_1	Full level	α	-	-	-
$H_2 \cap H_3 \cap H_4$	Bonferroni splitting alpha	-	α/2	α/2	0

Intersection hypotheses	Test	H_1	H_2	H_3	H_4
$H_2 \cap H_3$	Bonferroni splitting alpha	-	α/2	α/2	-
$H_2 \cap H_4$	Full level	-	α	-	0
H_2	Full level	-	α	-	-
$H_3 \cap H_4$	Dunnett	-	-	α*	α*
H_3	Full level	-	-	α	-
H_4	Full level	-	-	-	α

*adjusted alpha using Dunnett's procedure

For all other secondary endpoints described below, estimates and confidence intervals will be presented, but no formal statistical testing will be conducted.

The same analyses as for the primary endpoint will be repeated for each subtype of VOC event (uncomplicated VOC, acute chest syndrome, hepatic sequestration, splenic sequestration and priapism) leading to healthcare visit as per AC and for the annualized rate of VOC managed at home as reported in the eCRF.

The number of participants free from VOC leading to healthcare visit as per AC will be presented.

The time to first occurrence of VOC leading to healthcare visit will be summarized by treatment using Kaplan-Meier methods. Median time, 25th and 75th percentiles along with 95% confidence interval will be summarized and Kaplan-Meier plots will be generated. A stratified Cox regression analysis will be used to estimate the hazard ratio (HR), along with 95% confidence interval. The time to first occurrence of VOC leading to healthcare visit will be defined as the time from the date of randomization to the date of the first occurrence of the VOC as per AC. In the absence of a VOC leading to healthcare visit, participants will be censored at the time of the end of the primary observation period.

The same analyses will be repeated for the time to second VOC leading to healthcare visit. The time to second occurrence of VOC leading to healthcare visit will be defined as the time from date of randomization to the date of the second occurrence of VOC leading to healthcare visit as per AC. In the absence of two VOCs leading to healthcare visit, the participant will be censored at the time of the end of the primary observation period.

The mean duration of VOC leading to healthcare visit in days (defined as end date of the VOC per AC - start date of the VOC per AC + 1) will be described by treatment arm.

The same analyses as for the primary endpoint will be repeated for the annualized rate of clinic, hospitalizations and ER visits (both overall and VOC-related) and for the annualized rate of days of clinic/ER/hospitalization (both total and VOC-related).

SCD-related renal damage

Renal function tests will be analyzed similarly to the laboratory data and as described in Section 12.5.2. In addition change from baseline will be presented.

Long-term efficacy

The annualized rate of VOCs (leading to healthcare visit, managed at home and all) after 5 years of treatment post randomization will be summarized descriptively by groups in the FAS. The number and percentage of participants free from VOC leading to healthcare visit will be presented. Summaries will be provided for the corresponding annualized rate of VOC overall and per year and for the corresponding change from baseline.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 105 days after last dose of study medication (or until EOT date for participants continuing crizanlizumab after their EOT via commercial supply or post-trial access program).
3. Post-treatment period: starting at day 106 after last dose of study medication (or after EOT date for participants continuing crizanlizumab after their EOT via commercial supply or a post-trial access program).

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

Adverse events

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

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

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

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

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

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

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

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

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

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

For laboratory tests where grades are defined by CTCAE v5:

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

For laboratory tests where grades are not defined by CTCAE v5:

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

Microscopic urinalyses tests will be provided in listings only.

For hemoglobin parameter, summary and box plot of the absolute change from baseline over time will be provided.

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

Specific analyses to assess the impact of the renal (as part of efficacy) and liver function tests will be performed and described in the analysis plan.

Immunogenicity

Immunogenicity will be characterized descriptively tabulating ADAprevalence at baseline and ADA incidence on-treatment.

Other safety evaluations

Vital signs

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

Growth and sexual maturation

Data on growth and sexual maturation (Tanner stage) will be tabulated and listed for adolescents.

12-lead ECG

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

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

12.5.3 Pharmacokinetics

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

The inter-participant variations and CV% will be presented for the PK parameters. The point estimate and the corresponding two-sided 90% confidence interval (CI) for the mean of the log-transformed PK parameters after single dose and multiple doses will be derived respectively in each treatment group. 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 12-1 except Tmax, where only n, median, minimum and maximum will be presented since it is generally evaluated by a nonparametric method. Zero concentrations will not be included in the geometric mean calculation. The descriptive statistics will also be presented by the dose and age groups (adolescents and adults).

The PAS1 for 5.0 mg/kg and 7.5 mg/kg treatment groups will be used for all PK analyses described above.

Table 12-2 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 ($time^{-1}$)
$T_{1/2}$	The half-life during a dose interval (time)

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

In addition, the mean (+/- SD) and median 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.

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

The PAS2 for 5.0 mg/kg and 7.5 mg/kg treatment groups will be used for these PK analyses.

Crizanlizumab concentrations may be integrated into a population pharmacokinetic model. Details of the analysis methods will be developed in an independent modeling analysis plan and will be documented in a separate report document.

12.5.4 Pharmacodynamics

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 by treatment group. 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 will also be presented by the dose and age groups (adolescents and adults).

The PDS1 for 5.0 mg/kg and 7.5 mg/kg treatment groups will be used for all PD analyses described above.

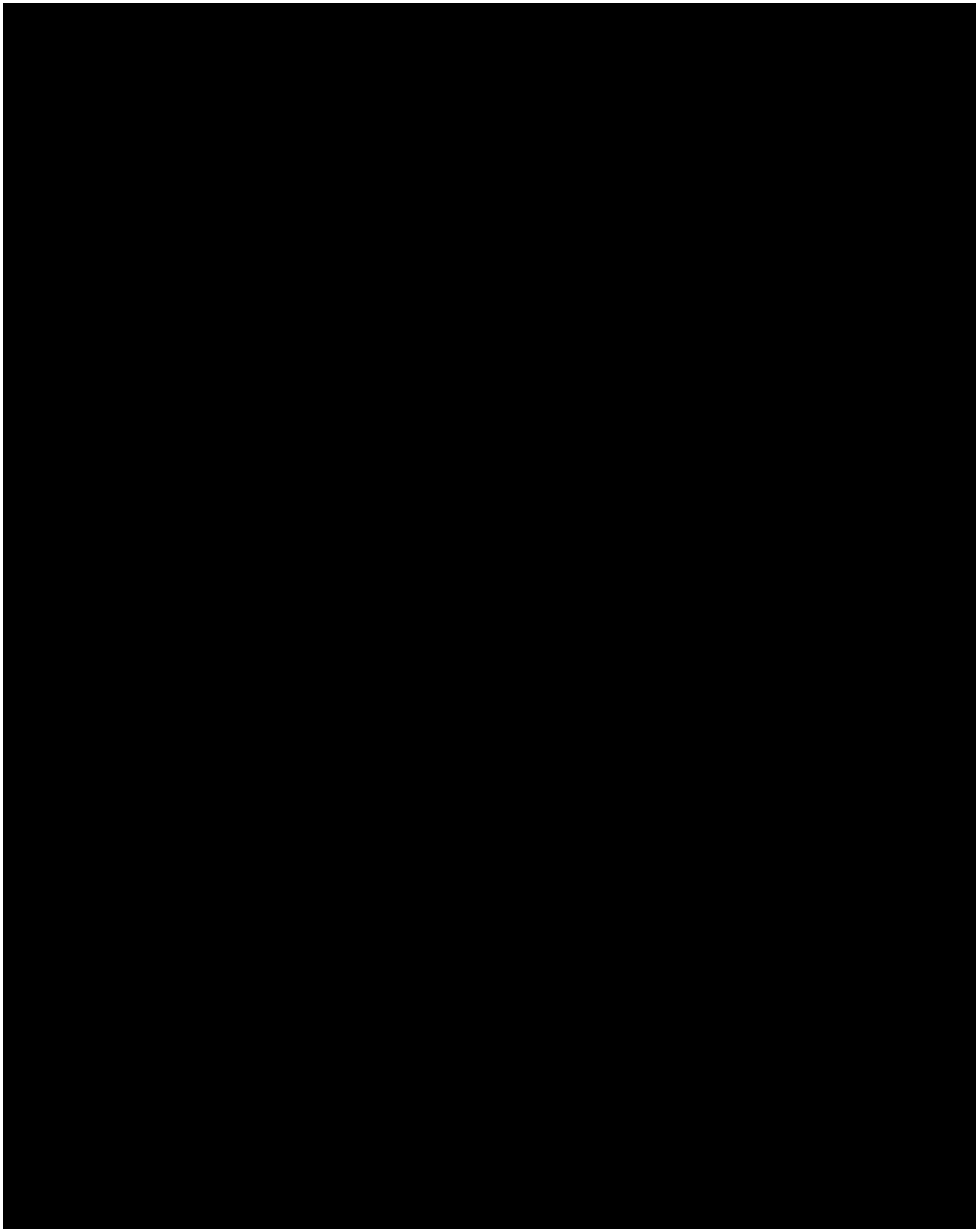
Descriptive statistics for PD inhibition will be presented at each scheduled timepoint.

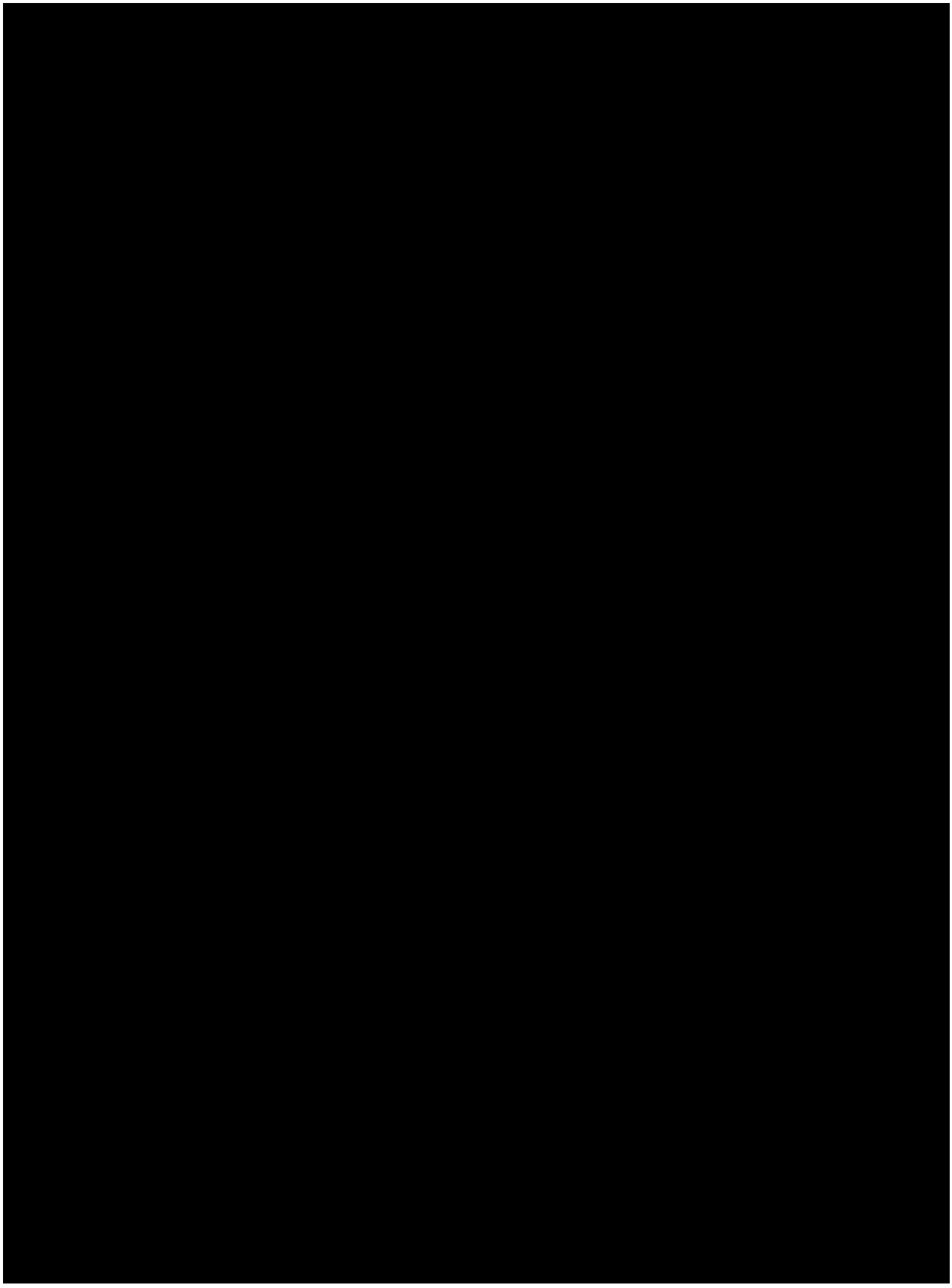
In addition, the mean (+/- SD) and median PD-time profiles over time will be displayed graphically on the linear and semi-log view.

All individual PD parameters and PD data will be listed.

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

The PDS2 for 5.0 mg/kg and 7.5 mg/kg treatment groups will be used for these PD analyses.





12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary variable annualized rate of VOCs leading to healthcare visit over the first year post randomization. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2 and Section 12.5.1.

Based on available data from SUSTAIN study, the mean VOC rate was 3.74 in placebo group and the ratio of VOC rate between 5.0 mg/kg and placebo was 0.65 (both estimates from a negative binomial regression with treatment, HU/HC use, and VOC rate in 12 months prior to screening (2-4 vs ≥5-10 VOC) as covariates).

Assuming a true treatment difference between crizanlizumab (7.5 mg/kg and 5.0 mg/kg) and placebo in the annualized rate of VOC of 35% over the first year of treatment, a sample size of 240 participants provides 90% power that the primary analysis will be statistically significant at the two-sided 5% significance level. This calculation assumes 1:1:1 randomization ratio and a dispersion parameter of 0.5 for all treatment groups. These calculations were made using power calculation based on normal approximation and Dunnett's adjustment and software SAS (9.4).

12.8.2 Secondary endpoint(s)

To assess the number of pediatric participants evaluable for PK trial simulations, following the recommendations from Wang et al (2012) for pediatric participants, have been performed and revealed a need of 16 participants with evaluable PK per dose group based on an expected interparticipant coefficient of variability for NCA AUC CV% (AUClast)= 59.89%, a need of 27 participants across dose groups based on the expected variability of popPK parameters, and 27 participants per dose group to achieve a precision of 20% for the 90% confidence interval of PK AUC assuming an estimated standard deviation of 0.554 for the log-transformed NCA AUC.

Given the uncertainties around the expected NCA AUC in pediatric participants, more weight is given to the popPK approach suggesting an overall need of 27 adolescent participants across different doses.

Assuming 27 participants evaluated for PD the precision for the PD-AUC is expected to be sufficiently high (11.5%).

Assuming a drop-out rate of 20% and a 1:1:1 randomization to placebo:5mg/kg:7.5mg/kg dose group, 48 adolescents need to be randomized.

13 Ethical considerations and administrative procedures

13.1 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, Art. 3 Par. 2 of the Directive 2005/28/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visits) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT, etc.).

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

13.4 Quality Control and Quality Assurance

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

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

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

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis/Sponsor.

- Thank You letter
- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication
- Trial Feedback Questionnaires (TFQ) - end of trial

14 Protocol adherence

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

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

14.1 Protocol Amendments

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

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

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should

be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References (available upon request)

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16 Appendices

Not applicable.